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Dosimetric analysis and clinical utility of sliding window imrt and 3D-CRT in prostate cancer: A treatment planning study

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ABSTRACT

Background: Advances in radiotherapy techniques have enabled the possibility of more accurate dose delivery to the Planning Target Volume (PTV) and limiting dose to Organs At Risk (OARs). The present study aimed to evaluate and compare dosimetric parameters using the Anisotropic Analytical Algorithm (AAA) in the Eclipse Treatment Planning System (TPS) between 3-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity-Modulated Radiotherapy (IMRT) techniques for prostate cancer patients. ***Materials and Methods:*** 3D-CRT and sliding window IMRT plans were produced for 100 prostate cancer patients before prostatectomy in the Eclipse TPS. The dose coverage of PTV, volume-dose constraints for OARs, conformity, and homogeneity indices were assessed from the dose-volume histogram (DVH). Dosimetric parameters were compared by Statistical Analysis Software. ***Results:*** The maximum dose delivered to PTV was a higher value with sliding window IMRT than 3D-CRT (p-value<0.001). Based on the ability to perform tumor dose escalation in IMRT plans, this technique provided higher values of D_{mean}, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ and $D_{2\%}$ than 3D-CRT. Volume-dose parameters (V_{15}, V_{25}, V_{35} and V50) for the rectum, bladder, and femoral heads were significantly reduced in IMRT technique. Compared with 3D-CRT, dose distributions of IMRT plans were less homogeneous. The conformity index was obtained better for IMRT plans(p-value<0.001). ***Conclusion:*** IMRT plans significantly improved dosimetric values of PTV and resulted in better target coverage and inhomogeneity of dose distributions as well as led to decreased volumes irradiation of critical organs than 3D-CRT plans. Therefore, IMRT technique is recommended as the first choice to improve treatment planning for prostate cancer patients.

INTRODUCTION

Prostate cancer is the most significant type of cancer and the second leading cause of cancer mortality among men. According to a report from the American Cancer Society, 288,300 new cases of prostate cancer will be diagnosed in the United States, and 34,700 will die from the disease in 2023 [(1)]. Many patients are asymptomatic within the early stages, and the presence of symptoms typically indicates locally advanced or metastatic disease. Symptoms include difficulty starting or stopping urination, frequent urination, blood in the urine, and pain or burning with urination [(2)]. Based on the stages of the disease and other medical conditions, surgery, hormone therapy, chemotherapy, and radiotherapy are conclusive therapies for prostate cancer [(2, 3)]. Currently, radiotherapy is widely used alone or in combination with other treatment methods as a definitive and effective treatment to target cancer cells. The purpose of developing radiotherapy is to deliver a high therapeutic radiation dose to PTV and protect critical structures around the target [(4)]. IMRT and 3D-CRT with Image-Guided Radiotherapy (IGRT) are the most appropriate treatment techniques for localized prostate cancer in Iran. IMRT uses Multi-Leaf Collimators (MLCs) and many beamlets to optimize the delivered non-uniform radiation beam intensities. It utilizes advanced treatment planning algorithms to optimize the intensity of radiation beams, allowing for precise dose delivery to PTV while minimizing radiation to OARs. Other advantages of IMRT include tumor dose escalation, better target coverage, excellent conformity index (CI) of PTV, reduced radiation toxicity to OARs around PTV, and beam energy less than 10 MV than older treatment techniques such as 3D-CRT [(4-8)]. Further, the IMRT technique enables treating patients using step-and-shoot (SS) and dynamic or sliding windows (SW). The radiation beam is modulated through the continuous movement of MLCs in the SW technique [(5)]. The increased monitor units (MU) and longer treatment delivery time in IMRT plan than 3D-CRT could increase the leakage from collimator

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leaves and scattered radiation. Indeed, an increase in collimator scatter might cause a rise in the risk of carcinogenic [8]. The main purpose of this investigation was to compare the dosimetric advantages and disadvantages of sliding window IMRT and 3D-CRT plans to assess the appropriate radiotherapy technique for prostate cancer patients.

MATERIALS AND METHODS

Patient preparation

We investigated 100 patients diagnosed with prostate cancer. All patients were selected before prostatectomy. Before CT simulation and setup, immobilization was done using the MacroMedics OmniBoard™(Moordrecht, The Netherlands). Patients were supine with arms on the chest. This situation causes dose reduction to OARs and is comfortable for the patient. The CT images are taken with Neusoft CT scan (Neusoft Medical Systems Co., Ltd, Shenyang, China) a slice thickness of 5 mm from the mid sacroiliac joint to 1 cm under the anus to include the rectum, femoral heads, bladder, and prostate gland for each patient. The image data with DICOM (Digital Imaging and Communications in Medicine) format were imported into the Eclipse TPS version 15.2 (Varian Medical Systems, Palo Alto, CA, USA) for contours of the Gross Tumor Volume (GTV), the Clinical Target Volume (CTV), PTV, and OARs.

Target volumes and OARs delineation

Accurate delineation of target and OARs is one of the essential steps in treatment planning that a radiation oncologist performs on CT images using the Eclipse TPS. The GTV was determined as the whole prostate. A 1-cm margin was applied to the GTV to generate the CTV, but to decrease the dose to the rectum, the posterior margin was reduced to 5 mm. The target tissue volume containing CTV with a 5 mm margin was delineated as PTV. OARs such as the rectum, bladder, and femoral heads are contoured on CT images.

Treatment planning

All treatment plans were produced using the Eclipse TPS, and dose distributions were computed by the AAA algorithm. 3D-CRT treatment plans were created in two phases. The prescription dose was 70.3 Gy / 35 fractions. In the first phase, each plan was arranged based on the 4-field box technique, including the standard axial anterior, posterior, and lateral beams with 15 MV photon energy, and the gantry angles of 0°, 90°, 180° and 270° were selected (figure 1A). The second phase was planned using non -coplanar photon beams with different gantry angles (figure 1B). Finally, phases 1 and 2 were utilized for the plan evaluation. For the inverse planning systems (IMRT), treatment consisted of seven fields with 0°, 50°, 100°, 152°, 202°, 252° and 302° gantry angles and using 6 MV photon energy (figure 2). Optimization aims to deliver the prescription dose to PTV and reduce toxicities to OARs.

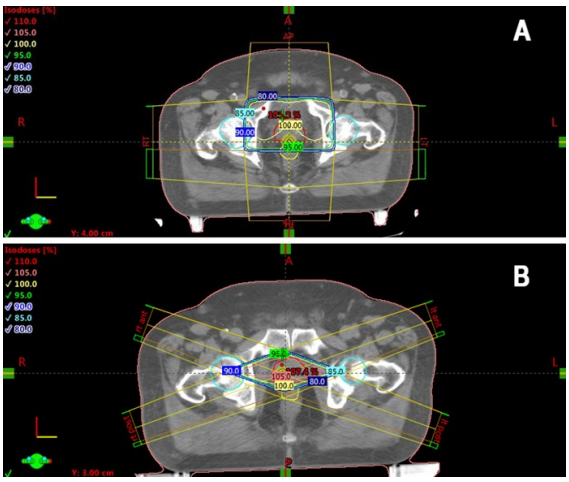

Figure 1. The beam arrangement and dose distributions of the 3D-CRT plan: **A)** Axial view of planning phase 1, **B)** Axial view of planning phase 2.

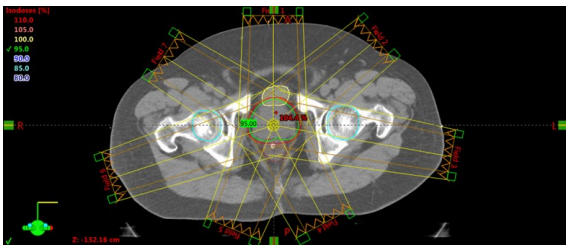

Figure 2. The beam arrangement of the IMRT plan.

This study achieved the optimization process based on the Radiation Therapy Oncology Group (RTOG) protocol for each IMRT plan (table 1). According to this protocol, the total dose to PTV was 79.2 Gy/ 44 fractions. Table 1 lists the optimization parameters, including the PTV and OARs (rectum, bladder, and femoral heads) dose constraints per RTOG protocol. After optimization, dose distribution was computed by using the AAA algorithm in the Eclipse TPS. After the treatment plan and dose calculation, the main step was to collect and import all data into the 3D-Slicer software (version 4.11, United States). Therefore, the dosimetric parameters, including V_{15}, V_{25}, V_{35}, and V_{50} for OARs (rectum, bladder, and femoral heads) as well as D_{mean}, D_{max}, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ and $D_{2\%}$ for PTV were obtained using the RTslicer module in the 3D-Slicer software.

Table 1. Dose-Volume constraints as per RTOG for IMRT plans.

Organs	Dose Constraints
PTV	$V_{79.2Gy}\geq 98\%$ $V_{84.7Gy}\leq 2\%$
Bladder	$V_{80Gy}\leq 15\%$ $V_{75Gy}\leq 25\%$ $V_{70Gy}\leq 35\%$ $V_{65Gy}\leq 50\%$
Rectum	$V_{75Gy}\leq 15\%$ $V_{70Gy}\leq 25\%$ $V_{65Gy}\leq 35\%$ $V_{60Gy}\leq 50\%$
Femoral Heads	$V_{50Gy}=0\%$

RTOG, Radiation Therapy Oncology Group; PTV, Planning Target Volume.

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Conformity (CI) and homogeneity indices (HI) are important dosimetric parameters for evaluation of various treatment plans. The homogeneity index was defined as the dose homogeneity inside PTV. Also, the conformity index was used to measure the conformation of prescription doses on PTV.

The homogeneity index was calculated for each plan by using equation 1:

$$HI = \frac{D2\% - D98\%}{D50\%} \quad (1)$$

Where $D_{2\%}$, $D_{98\%}$ and $D_{50\%}$ are the maximum dose received by 2%, 98%, and 50% of PTV. The conformity index was calculated by using equation 2:

$$CI = \frac{PTV_{95\%}}{PTV_T} \quad (2)$$

Where, $PTV_{95\%}$ is a volume of PTV that receives 95% of the prescribed dose and PTV_T is the total volume of PTV.

Statistical analysis

The dosimetric parameters between IMRT and 3D -CRT plans were evaluated and compared using Statistical Analysis Software (SPSS version 26, Chicago, IL, USA). All data were assessed for normality of distribution with the Skewness test. The Mann-Whitney U tests and the independent sample t-tests were used to analyze all data. Quantitative variables are demonstrated as mean and standard deviation. A p-value less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Table 2 and figures 3 and 4 show the results comparing dosimetric parameters as mean values ± the standard deviation (SD) between IMRT and 3D-CRT plans for PTV and OARs. The comparison of D_{max}, D_{mean}, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ and $D_{2\%}$, distributions of PTV between two radiotherapy methods are shown in figure 3A. The IMRT plans resulted in significantly higher maximum and mean doses and the dose delivered to 2%, 50%, 95% and 98% of target volume than 3D-CRT plans. Indeed, the mean dose received by target volume based on the prescription dose in 3D-CRT and IMRT plans ranged from 69.8 (SD±4.4) Gy and 80.59 (SD±0.74) Gy (99.2% and 101.7% of the prescribed dose), respectively. The average maximum doses delivered to PTV were 71.64 Gy and 84.35 Gy for 3D-CRT and IMRT plans (101.9% and 106.5% of the prescription dose). Based on dose escalation in IMRT technique, the D_{Max} was obtained more than 3D-CRT plan (P= 0.001).

Dosimetric outcomes of OARs (rectum, bladder, and femoral heads) are summarized in table 2 and figure 4. There were statistically significant differences (p-value<0.001) between the mean of both plans for the radiation dose to critical structures around PTV except for V_{50} of the rectum. The volumes of OARs that received doses in IMRT plans were less than the received volumes by 3D-CRT plans. The volumes of bladder receiving 15, 25, 35 and 50 Gy radiation doses were 23.8%, 27.3%, 35.6%, and 30.9% reductions in the IMRT treatment planning than 3D-CRT plans. Also, the percentage of the rectum volumes irradiated with 15, 25, 35 and 50 Gy doses were 25.5%, 26.6%, 28.2% and 23.2%, significantly lower using IMRT plan than 3D-CRT plan. In IMRT plans, similar results were obtained for femoral heads in the volumes irradiated. Therefore, IMRT treatment planning was better in sparing the critical structures around the prostate.The average homogeneity and conformity results of PTV are summarized in table 2 and figure 3B. A lower HI represents better homogeneous dose distribution in PTV, and the ideal CI, is equal to 1, indicating a highly conformal plan. The two treatment methods had statistically significant differences in homogeneity dose distribution, and dose conformity (p-value <0.001). The value of the homogeneity index was 0.09 for the IMRT plans, which was decreased to 0.07 for the 3D-CRT plans. Hence, HI in the IMRT treatment planning was 28.5% more than 3D-CRT plan. The conformity index were 0.967 and 0.969 for 3D-CRT and IMRT treatment planning. Therefore, the conformity index was slightly higher for IMRT plans than 3D-CRT plans.

Table 2. Comparison of Dosimetric Parameters for target volume and OARs between IMRT and 3D-CRT plans.

Variables	3D-CRT (mean ± SD)	SW-IMRT (mean ± SD)	p-value
PTV			
D_{Max} (Gy)	71.64 ± 3.05	84.35 ± 0.79	<0.001*
D_{Mean} (Gy)	69.8 ± 4.4	80.59 ± 0.74	<0.001*
$D_{2\%}$ (Gy)	71.51 ± 2.99	83.32 ± 0.45	<0.001*
$D_{50\%}$(Gy)	70.62 ± 2.9	81.2 ± 0.77	<0.001*
$D_{95\%}$(Gy)	67.22 ± 5.09	76.38 ± 0.88	<0.001*
$D_{98\%}$(Gy)	65.81 ± 6.16	75.01 ± 1.23	<0.001*
HI	0.07 ± 0.08	0.09 ± 0.01	<0.001*
CI	0.967 ± 0.05	0.969 ± 0.02	<0.001*
Bladder			
V_{15Gy} (%)	100	76.16 ± 22.67	<0.001*
V_{25Gy} (%)	98.86 ± 4.19	71.85 ± 23.47	<0.001*
V_{35Gy} (%)	97.05 ± 7.15	62.5 ± 23.26	<0.001*
V_{50Gy} (%)	59.87 ± 27.19	41.34 ± 17.02	<0.001*
Rectum			
V_{15Gy} (%)	99.19 ± 2.07	73.82 ± 17.54	<0.001*
V_{25Gy} (%)	95.71 ± 7.89	70.24 ± 18.03	<0.001*
V_{35Gy} (%)	88.2 ± 15.91	63.31 ± 18.2	<0.001*
V_{50Gy} (%)	46.59 ± 28.42	35.77 ± 12.13	0.06
Femoral Heads			
V_{15Gy} (%)	100	57.75 ± 24.03	<0.001*
V_{25Gy} (%)	95.36 ± 15	25.59 ± 19.83	<0.001*
V_{35Gy} (%)	71.28 ± 29.16	2.87 ± 6.98	<0.001*
V_{50Gy} (%)	19.6 ± 16.17	0.25 ± 2.38	<0.001*

*Statistically significant at p-value<0.05; PTV, Planning Target Volume; 3D-CRT, 3D Conformal Radiation Therapy; SW, sliding window; IMRT, Intensity-Modulated Radiation Therapy; HI, Homogeneity Index; CI, Conformity Index; SD, Standard Deviation

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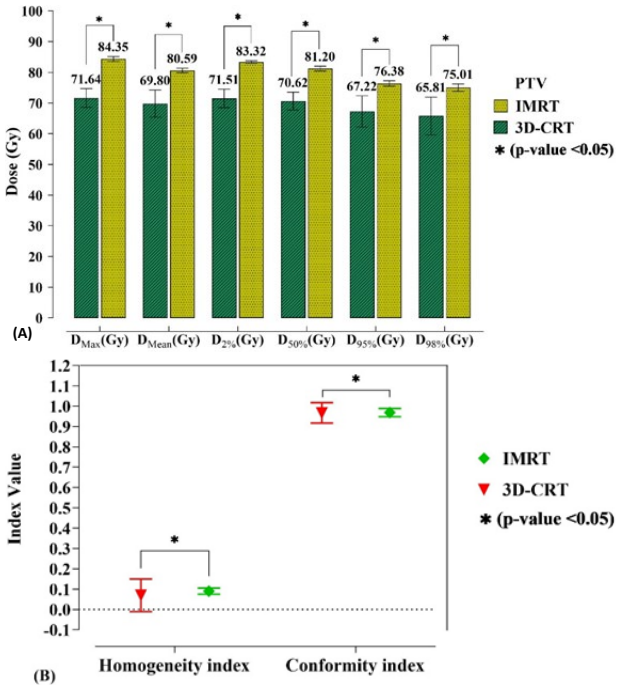

Figure 3. A) Comparison of dosimetric parameters for PTV between IMRT and 3D-CRT plans. **B)** the difference in conformity and homogeneity index between two treatment planning methods.

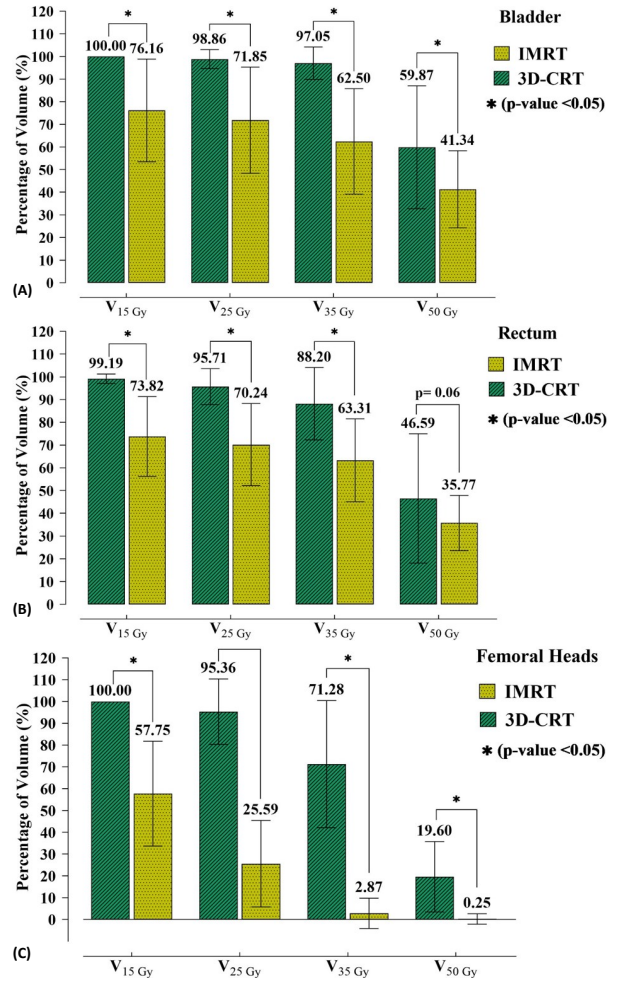

Figure 4. Comparison of dosimetric parameters for OARs between 3D-CRT and IMRT plans. **(A)** Bladder, **(B)** Rectum, **(C)** Femoral heads.

DISCUSSION

Advanced modulation radiation therapy (IMRT) provides better isodoses to the target without side effects by increasing the prescribed dose [6]. In this investigation, to assess the advantages and disadvantages of IMRT and 3D-CRT plans in prostate radiation therapy, comparisons of dosimetric parameters were made between two radiotherapy methods. In planning 3D-CRT for prostate cancer, the maximum dose may not always be located within the target volume because this plan is not optimum as the dose constraints. Therefore, in high radiation doses, a hot spot may be created outside the PTV and cause radiation-induced toxicities for surrounding normal organs. Also, using the 4-field box technique in 3D-CRT plans based on the anatomy of the prostate results in hot spots in OARs, such as the bladder and rectum [7-11]. Our results showed (table 2 and figures 3 and 4) using the optimization process in inverse planning (IMRT) significantly increased the level of radiation doses delivered to PTV (D_{mean}, D_{max}, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ and $D_{2\%}$) and reduced volumes of the bladder, rectum irradiated (V_{15}, V_{25}, V_{35} and V_{50}) compared to the 3D-CRT plans. As one might expect from the results, the IMRT plan effectively reduces hot spots and improves target volume coverage as well as dose distribution in PTV. Based on previous studies, using optimization in IMRT treatment planning causes to delivery of more radiation doses to PTV and allows better protection of OARs. In the research of Bhardwaj *et al.*, IMRT and 3D-CRT treatment plans were evaluated, including 24 patients diagnosed with localized prostate cancer. Their research indicated that the IMRT plans provided better protection for critical organs like the rectum and bladder than the 3D-CRT plans [12].

The ability to obtain a greater degree of conformity of dose distribution to PTV with reduced dose to the OARs and better control of dose homogeneity was evaluated by using conformity and homogeneity indices [12,13]. We used $D_{98\%}$ and $D_{2\%}$ in PTV as a measure of the dose uniformity or homogeneity index (HI). Indeed, a lower homogeneity value or HI closer to 0 is the baseline for more homogeneity and represents a better homogeneity in PTV. The difference in HI (figure 3B) between the radiotherapy methods showed greater homogeneous dose distributions to PTV in 3D-CRT than IMRT. This means more nonuniformity of dose distribution in IMRT plans, which led to decreased radiation doses to OARs around PTV (rectum, bladder, and femoral heads). The ideal conformity index (CI=1) indicates a highly conformal plan. If the value of CI is greater than 1, the critical structure has been irradiated; when CI is less than 1, the target volume is partially irradiated [13]. In this study, the IMRT plan provided a bit better conformality of 95% isodose to the target volume than 3D-CRT (table 2 and figure 3B).

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Therefore, IMRT caused better coverage of the PTV.

The important point about prostate cancer is the $\frac{\alpha}{\beta}$ ratio. It illustrates the curviness of the cell survival curve and the sensitivity of a particular cancer cell to irradiation. α and β are radio-sensitivity parameters related to single-hit (a non-repairable kind of damage) and multiple-hit(repairable) damages, respectively [14, 15]. A high $\frac{\alpha}{\beta}$ is not sensitive to variation in fraction size and indicates little repair or irreparable damage, but in contrast, a low $\frac{\alpha}{\beta}$ (high repair) is very sensitive to an increase in fraction size. The $\frac{\alpha}{\beta}$ value for prostate cancer cells is lower (~ 1.5 Gy) than other cancer cells [4, 16, 17]. Hence, prostate cancer cells are late-responding and sensitive to increases or variations in fraction size. Figure 3A shows that IMRT plan produced higher dose values with significant differences compared to 3D-CRT plan (P= 0.001). Therefore, IMRT delivered more doses inside PTV, which led to improvement in the tumor control probability (TCP) [15, 18].

According to the biological features of prostate cancer, the dose escalation in IMRT plan is effective in treating the prostate cancer. The rectum and bladder volume often receive radiation doses during the treatment of pelvic malignancies such as prostate cancer [19]. Therefore, it is important to choose the right method to reduce the toxicity of these organs. The $\frac{\alpha}{\beta}$ ratio for the rectum and bladder are 2.5 to 5 Gy and 3 to 7 Gy, respectively [14].

Indeed, these organs are sensitive to high doses and behave as late-responding tissue. For 3D-CRT and IMRT, dose constraints to the rectum, bladder, and femoral heads were considered by RTOG and QUANTEC. The data in table 2 and figure 4 show, that there were significant differences between OARs volumes that received doses of 15, 25, 35, and 50 Gy. Indeed, the mean volumes of critical structures around PTV were significantly lower than 3D-CRT treatment planning. This condition can be caused by dose constraints, which limit dose to OARs (the rectum, bladder, and femoral heads). The results of previous studies showed [20-24] that the IMRT treatment planning delivered high radiation doses and irradiated significantly less volumes of OARs than 3D-CRT in treating prostate cancer. In the study of Al Shareef *et al*. IMRT was more effective than 3D-CRT in sparing organs at risk and had a better CI, whereas 3D-CRT showed a better HI than IMRT. This research suggested utilizing IMRT with 6 MV for prostate cancer treatment, and 3D-CRT was recommended as an alternative treatment option [23].

Hence, the risk of normal tissue complication is reduced by reducing the irradiated volume. In the investigation by Viani *et al.,* late genitourinary (GU) and gastrointestinal (GI) side effects due to IMRT and 3D-CRT techniques for prostate cancer patients were assessed. After a follow-up period of 51 months, the highest incidence of late GU was 13.1% in IMRT and 15.4% in the 3D-CRT. The highest incidence of late GI was 10% for IMRT and 24% for 3D-CRT. IMRT lowered the risk of late GU and GI symptoms than 3D-CRT [25]. Hence, IMRT has better protection for these organs and reduces the risk of complications of prostate radiation therapy.

CONCLUSIONS

Compared to the 3D-CRT technique, inverse planning IMRT as a powerful instrument facilitates the reduction of the dose delivered to OARs around the target and causes higher radiation dose to PTV. In this study, the utilization of optimization in the IMRT plan was necessary to achieve a better-quality plan compared to 3D-CRT. Our results indicate that IMRT optimization reduces the irradiation volume of the bladder, rectum, and femoral heads at variation doses (15, 25, 35 and 50 Gy), avoids radiation toxicity, reduces hot spot, and delivers more doses to the target volume.

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***Author contribution*:** M.M. and A.N. wrote the original draft of the manuscript, collected and analyzed data, and interpreted the results. M.A.B. and R.D. reviewed and edited the manuscript.

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