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New radiobiological comparison of intensity-modulated radiation therapy prostate plans of seven and five fields

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► ***Original article***

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ABSTRACT

Background: Based on recently published studies carried out in various institutions, the dosimetric evaluation was conducted to compare 5 and 7-field intensity-modulated radiation therapy (IMRT) plans. So far, dosimetric indexes have been used as the main parameters. The present study is new, it uses more sophisticated tools of evaluation based on radiobiologic indices as recommended. ***Materials and Methods:*** A comparative study of five and seven fields IMRT plans of sixteen randomly chosen prostate cancer cases has been evaluated radiobiologically. The modified Poisson model of Marsden allows us to calculate the tumor control probability (TCP) of the treated planning target volume (PTV60); The Lyman–Kutcher–Burman (LKB) model is used to calculate normal tissue complication probability (NTCP) of the organs at risk (rectal wall, bladder wall and femoral heads). We have elaborated an in-house program RADBIOFOR to calculate TCP and NTCP and use the dose volume histograms (DVH) from the treatment planning system (TPS) as input information. ***Results:*** A significant statistical difference was observed for the bladder (P-value=0.045). The statistical analysis for the rectum did not show a difference (P-value= 0.234). Meanwhile, 88% of the cases exhibited slightly lower toxicities with the 7-field compared to the 5-field. ***Conclusion:*** The present study recommends using a 7-field IMRT plan since it has proved to predict lower toxicities in the bladder and the rectum wall even though the 5-field predicts minor improvements in the local control in the tumor compared to the 7-field.

INTRODUCTION

The third cancer after those of the lungs and colon to affect men is prostate cancer, this type of cancer affected some 2.3 million Algerians at the end of 2011 and is still growing until 2024 [1]. The major treatment for localized prostate cancer is radiotherapy. Based on large clinical experiences the intensity modulated radiation therapy delivers a very conformal radiation dose in the often-concave target volume while limiting the dose to the rectum and bladder wall compared to a standard 3DCRT [2-4]. In addition, the optimization process and MLC (multi-leaf collimators) movement provide a well-shaped intensity distribution providing a good tumor covering of cancer [5, 6]. Prostate IMRT uses 5 to 7 fields for treatment. While, the TPS (Treatment planning system) divides each beam into a large number of sub-beams (beamlets) and determines the best and optimum settings for their energy flow or beam weight, and the intensity of each beamlet can be modified individually.

In recent years, several studies have been carried out to compare the effectiveness of 5 and 7-field plans [7, 8]. However, according to the available literature, none of these studies utilized the radiobiological tool during their research analysis. Although, radiobiology is an essential tool in evaluating and optimizing radiation treatment planning, it is crucial to support dosimetric evaluation by predicting toxicities and calculating new criteria for treatment evaluation plans. The second objective of this study was to determine the most effective plan for prostate IMRT treated with a hypofractionation regimen that would minimize the risk to the surrounding organs. However, the usual doses for treating prostate cancer are between 70 to 80 Gy for exclusive radiotherapy depending on the technique used and according to the clinical context, and between 60 to 66 Gy for postoperative radiotherapy (2 Gy per session/5 sessions per week) [9]. Radiotherapy can involve up to 33 sessions, with each session lasting no more than 10 minutes. Due to weekend breaks and international treatment standards, the number of patients who can be treated daily with the same device is limited. Additionally, based on Brenner and Hall's analysis [10] it was assumed that treatment of early cancer is highly sensitive to tumor size, therefore it is crucial to consider the clinical stage when determining the appropriate treatment regimen. Hypofractionation regimen is not suitable for advanced prostate cancer

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characterized by T3-T4. Significant segmentation sensitivity was quantified by the alpha/beta value of a linear squared model of prostate cancer estimated to be 1.5 Gy, which might increase sensitivity to a higher dose per fraction. This estimation was confirmed after that by a large number of studies [11-13]. For this reason, hypofractionation is presented as a solution to improve access to care and increase the quality of care. Furthermore, moderately hypofractionated radiation therapy was equally effective compared to conventional treatment regimens for prostate cancer and improved biochemical or metastatic control with minimal toxicity [14, 15]. The used regimen in this study was proposed by Fowler *et al.* [9] who provided a therapeutic gain of 7% compared to a conventional regimen [10]. Then, Catton *et al.* [16] in turn compared this regimen to the standard 78 Gy with 39 fractions and 74 Gy with 37 fractions, successively. The results were cited as non-inferior to the standard regimens. Moreover, the 60 Gy regimen with a 20-session is recommended as a new standard of care for external-beam radiotherapy of low and intermediate-risk prostate cancer [17, 18] with new dose constraints of V46 Gy ≤ 30% and V37 Gy ≤ 50% for the rectum wall and V60 Gy ≤ 5%, V48 Gy ≤ 25%, and V41 Gy ≤ 50% for the bladder wall [19]. Our comparison between the two techniques, using dosimetric indexes evaluation was not sufficient to investigate differences between the 5-field and 7-field IMRT technique.

As new, this study aimed to provide a comprehensive radiobiological evaluation of the outcomes of the 5 and 7-fields IMRT plans and their effectiveness in controlling tumor targets and preserving organs at risk. The second main objective of this study was to determine the most effective plan for prostate IMRT treated with a hypofractionation regimen that would minimize the risk to the surrounding organs.

MATERIALS AND METHODS

Treatment planning

In this retrospective study, a group of sixteen patients randomly chosen with low and intermediate-risk prostate cancer were treated on Varian linear accelerators (Varian Medical Systems, Inc., Palo Alto, CA, USA) in the radiation therapy center in Setif (Algeria). The 5 and 7-fields IMRT technique was used with 60 Gy given in 20 fractions; all of them received hormone therapy simultaneously with radiotherapy. As an illustration, the patient's average age was 62.5 years (ranging from 45 to 80 years old), and the average prostate-specific antigen (PSA) was estimated to be 14.5 ng/mL (between 4-25 ng/ml), while the Gleason scores ranged from 6 to 9.

The treatment plans were generated using 18 MV energy for both 5 and 7-field; the entering angles were different between the two fields. We used the arrangement with gantry angles of 36°, 100°, 180°, 260°, and 324° associated to the LAO, LPO, Posterior, RPO and RAO for 5-field plan treatment, respectively; However, for 7-field, 0°, 40°, 80°, 120°, 240°, 280° and 320° were associated to the Anterior, LAO_1, LAO_2, LPO, RPO, RAO_2, and RAO_1, respectively see (figure 1). The priority which defined the importance of the objectives with other optimization objectives was between 0 and 1000. The minimum number of points recommended in the structure is 2000. The point cloud resolution for structures 5000 cm^3 or smaller is between 1-3 mm, but structures greater than 5000 cm^3 have a resolution of 4.5 mm [17]. The plans have been validated using usual dosimetric evaluations, including the conformity index, homogeneity index, and similarity index on the TPS [14, 20].

The plans are approved, and the next step consists of generating the DVH needed as input for our radiobiologic analysis. In the next section, the models used to predict TCP and NTCP values are described in detail.

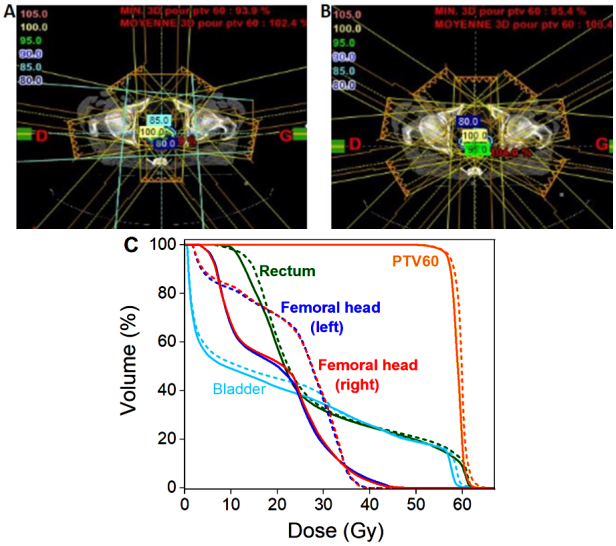

Figure 1. (A) Radiotherapy treatment planning system showing a view of prostate case planification using 5-field IMRT technique. Isodose from 80% to 100 % are shown. **(B)** Same patient using 7-field IMRT technique. Isodose from 80% to 100 % are also shown. **(C)** DVH resulting from 5-field and 7-field techniques are plotted together for PTV60, rectum, bladder and the two femoral heads. Dose prescription is 60 Gy/3 Gy daily fraction, 20 fractions excluding the week ends.

Radiobiological indexes: TCP (modified Poisson model -Marsden model)

The TCP model given in (equation 1) describes tumor control probabilities based on two assumptions: each tumor is composed of a given number of clonogenic cells, and a tumor is locally controlled if all its clonogenic cells are killed. This model was derived using Poisson statistics and the Linear Quadratic (LQ) model [21, 22].

Population variability in radiation sensitivity was

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incorporated into the model. This is simulated as a Gaussian distribution of α_j values with mean α and standard deviation σ_α [23].

$$TCP=\sum_j g_j(\sigma_\alpha)\prod_i \exp[-\rho v_i \exp[-\rho v_i \exp(-\alpha_j D_i(1+\beta/\alpha d_i))]] \quad (1)$$

We can assume that the tumor volume is given by a series of sub-volumes v_i with a clonogenic density ρ_{cl} receiving a uniform dose D_i; α is the radiosensitivity of the tumor with a standard deviation σ_α; Their corresponding values are given in table 1 [24, 25].

Table 1. The identified parameters used in equation 1 for tumor control of the PTV60 for early and intermediate adenocarcinoma prostate cancer [24, 25]. ρ_{cl} is the clonogenic density; α is the radiosensitivity of the tumor with a standard deviation σ_α. α/β is the tumor intrinsic radiosensitivity.

Marsden model	Model parameters
PTV60 (Tumor control)	α (Gy^{-1}) = 0.155 σ_α (Gy^{-1}) = 0.058 α/β (Gy) = 1.5 ρ_{cl} (cm^{-3}) = 10^7

Radiobiological indexes: NTCP (The Lyman–Kutcher–Burman model)

The most used model in the calculation of the probability of complications of normal tissues is the Lyman–Kutcher–Burman (LKB) NTCP model [26-28]. This model consists of three equations (2, 3, and 4):

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{\frac{-X^2}{2}} dX \quad (2)$$

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}} \quad (3)$$

$$D_{eff} = \left(\sum V_i D_i^{1/n}\right)^n \quad (4)$$

We have used the nearly-best rational approximations to evaluate the error function given by the (equation 5) provided by Cody (1969) [29].

$$NTCP = \frac{1}{2}\left[1 + erf\left(\frac{t}{\sqrt{2}}\right)\right] \quad (5)$$

Where; D_{eff} is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution; TD_{50} is the dose that produces a 50% probability of response; m is the slope of the response curve; n is a parameter reflecting the biological properties of the organ, indicating volume dependence; vi is the relative volume of voxel i compared to the reference volume. The identified parameters of different endpoints for each organ at risk (Severe proctitis/necrosis/ stenosis/fistula of rectum wall and symptomatic bladder contracture and volume loss of bladder wall) used in this analysis are given in table 2 [27].

The biological models described above with their corresponding parameters have been implemented in our elaborated in-house program Radbio-For. It uses as input the DVH of the PTV60 and organs at risk and critical structures in both formats, cumulative or differential. We carefully tested our code by comparing the results of TCP and NTCP models with RADBIOMOD [23] and BioSuite [24].

Table 2. NTCP model parameters of rectum and bladder wall of severe proctitis/necrosis/stenosis/fistula and symptomatic bladder contracture and volume loss, respectively (27). TD50 is the dose that produces a 50% probability of response; m is the slope of the response curve; n is a parameter reflecting the biological properties of the OAR; α/β is the intrinsic radiosensitivity of the OAR.

LKB parameters	n	m	TD50	α/β
Rectum wall (Severe proctitis/ necrosis/stenosis/fistula)	0.12	0.15	80	3
Bladder wall (Symptomatic bladder contracture and volume loss)	0.5	0.11	80	3

Statistical analysis

Results of the two sets, i.e. 5-field and 7-field IMRT plans, have been compared using non-Mann-Whitney parametric statistical tests (Addinsoft XLStat 2020 software). The null hypothesis was considered when the two sets of results were equal; the bilateral alternate hypothesis was considered when they were different with a confidence interval of 95% on the normal distribution. Exact P-value was calculated. A value of $P<0.05$ was considered to reject the null hypothesis (the difference between the two data sets is statistically significant). Note that in the case where the bilateral alternate hypothesis is considered, we added the absolute difference by subtracting the TCP or NTCP values of the two plans to identify the best technique. Moreover, when the null hypothesis is considered, this difference can only be used as an indicator by comparing the number of patients.

RESULTS

The TCP values calculated for the PTV using (equation 1) and parameters identified in table 1 are presented in figure 2 (A); the tumor control calculated is higher than 70% for most patients. The NTCP values calculated for the rectum using equations 2-5 and parameters listed in table 2 of severe proctitis/necrosis/stenosis/fistula [27] are presented in figure 3 (A); note that NTCP values are < 5% for all patients. Exception is outlined for NTCP of patient 8 but with minor importance; it exceeds the recommended threshold for both 5-field and 7-field techniques (NTCP>5%), most probably, due to difficulties in tightening dose constraints when planning treatment of a large tumor size. Similarly, we calculated the NTCP using equations 2-5 for the bladder and the parameters listed in table 2 of symptomatic bladder contracture and volume loss. The results are displayed in figure 4 (A); NTCP values for bladder are also very encouraging for all patients (<5%). Note that the value calculated for patient 10

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with the 5-field plan is higher than the 7-field but within the recommended range (<5%).

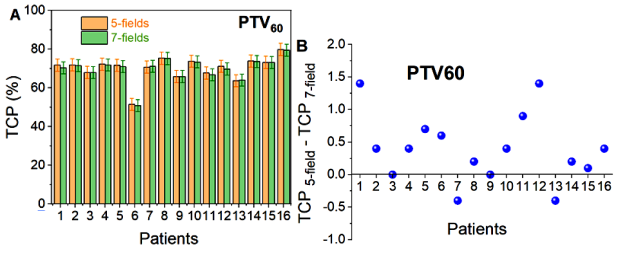

Figure 2. (A) TCP of 5-field and 7-field IMRT plan calculated for PTV60 of sixteen patients using parameters in table 1 (5-field: SD = 6.28, SE = 1.57; 7-field: SD = 6.27, SE=1.556). The computed P-value using non-Mann-Whitney parametric statistical tests was 0.635. **(B)** Absolute TCP values difference of 5-field and 7-field IMRT plan for PTV60 of sixteen patients.

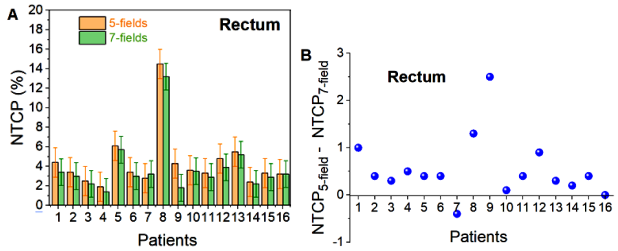

Figure 3. (A) NTCP of 5-field and 7-field IMRT plan calculated for rectum wall of sixteen patients using cited parameters in table 2 (5-field: SD = 2.97, SE = 0.75; 7-field: SD = 2.74, SE=0.68). The computed P-value using non-Mann-Whitney parametric statistical tests was 0.234. **(B)** Absolute NTCP values difference of 5-field and 7-field IMRT plan for rectum wall of sixteen patients.

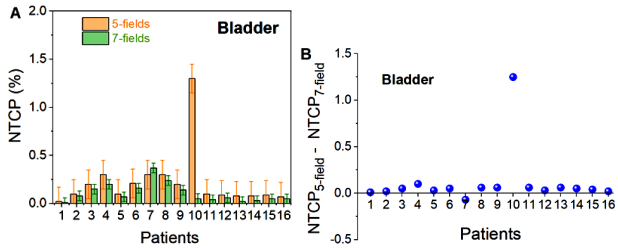

Figure 4. (A) NTCP of 5-field and 7-field IMRT plan calculated for bladder wall of sixteen patients using cited parameters in table 2 (5-field: SD = 0.3, SE = 0.075; 7-field: SD = 0.1, SE=0.025), the computed P-value using non-Mann-Whitney parametric statistical tests was 0.045. **(B)** Absolute NTCP values difference of 5-field and 7-field IMRT plan for bladder wall of sixteen patients.

The data presented in table 3 show the mean and standard deviation TCP and NTCP values for both five and seven fields. The calculated mean TCP value for 5 -field and 7-field IMRT plans (70% and 69%, respectively) agree well within the recommended value of TCP > 50% [30]. NTCP mean values and their corresponding standard deviations for both techniques are also within the recommended value of NTCP < 5% [19, 30].

Table 3. Mean and SD of calculated TCP and NTCP of PTV, rectum, and bladder wall for 5-field and 7-field IMRT plans of sixteen early and intermediate adenocarcinoma prostate cancer cases.

Radiobiological models	Mean	SD
TCP 5-field (PTV)	70.17	6.28
TCP 7-field (PTV)	69.77	6.27
NTCP5-field (Rectum)	4.34	2.93
NTCP7-field (Rectum)	3.79	2.74
NTCP 5-field (Bladder)	0.22	0.30
NTCP7-field (Bladder)	0.11	0.09

DISCUSSION

Comparisons of the 5-field and 7-field IMRT techniques are being evaluated using the P-value as a tool for statistical analysis. According to figure 2 (A), the P-value of 0.635 (> 0.05) for PTV indicates non-significant differences suggesting no statistically discernible distinction. In this case, for more investigations, we show the difference between TCP values of 5-field and 7-field in figure 2 (B); we note that 12 patients representing 75% of the total number of the considered cases have TCP for 5-field higher than that of the 7-field. This suggests that the 5 -field technique is slightly more effective in ensuring better local tumor control when compared to the use of the 7-field. Our finding is supported by Mahdavi's study [8], which favors this technique as it requires a lower number of monitor units (MU) compared to the 7-field technique.

For the case of Rectum shown in figure 3 (A), the statistical analysis indicates that there is no significant difference between the two techniques (P-value=0.234). Meanwhile, upon further investigation, the difference in NTCP values of the two techniques shown in figure 3 (B) indicates that 14 patients (88% of the total number) treated with the 7 -field technique exhibited lower NTCP values compared to values from the 5-field technique. Therefore, the 7-field technique provided a significantly higher success rate in terms of minimizing complications and proved to be more effective in preserving the rectum wall with a mean difference of 0.54 %.

NTCP values of 5-field and 7-field IMRT techniques for bladder wall shown in figure 4 (A) have been found statistically different with a P-value=0.045. Similarly, based on the difference between calculated NTCP values from both techniques represented in figure 4 (B), 94% of the cases have higher NTCP values for 5-field compared to 7-field. By applying the 7-field IMRT technique, the dose delivery to the bladder wall is reduced by a

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mean value of 0.11%, making it a better alternative to the 5-field technique.

Note that the left and right femoral heads have also been investigated in this analysis but have not been shown because their corresponding NTCP values for both techniques have almost zero values ranging from 10^{-5} % to 10^{-10} %.

This detailed study shows the radiobiological advantage of using the 7-field technique over the 5-field technique; it is slightly more time-consuming but reduces the probability of bladder toxicity. Meanwhile, it is important to mention that a hypofractionation regimen of 60 Gy/3 Gy, 20 fractions are used for the sixteen cases of early and intermediate adenocarcinoma prostate cancer; it reduces the total period of treatment of three weeks compared to the conventional therapy of 74 Gy/ 2Gy daily fraction.

It is of utmost importance to outline that the present radiobiologic study comparing the 5-field and the 7-field IMRT technique is new; indeed, resulting TCP and NTCP are new tools that shed more light on similar recent studies [7, 8] comparing the two techniques by using dosimetric indices only. The dosimetric comparison study [8] showed no statistically significant differences observed between the 5 and 7-field IMRT plans concerning the conformity index (CI) and inhomogeneity index (HI); however, MU differences were observed in favor of the 5-field IMRT plans. Further, the mean dose delivered to the OARs was very comparable. Similarly, the dosimetric comparison of reference [7] concluded that in terms of conformity index, homogeneity index and monitor units both 5 beam and 7 beam IMRT technique show non-significant difference. The two studies in [7, 8] did not reveal any noteworthy differences. The present radiobiologic comparison provided new results in terms of tumor control in the PTV60 and prediction of severe proctitis/necrosis/stenosis/fistula in the rectum and symptomatic bladder contracture and volume loss in the bladder.

CONCLUSION

According to the findings and statistical analysis of this study, calculation of radiobiological indexes TCP and NTCP revealed that the 7-field IMRT technique ensures less toxicity in the bladder wall (bladder contractor and loss volume) and the rectum (severe proctitis/necrosis/fistula) than the 7-field IMRT technique. As a conclusion, the 7-field IMRT technique is a more suitable option to treat early and intermediate adenocarcinoma prostate cancer.

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***Ethics approval*:** The present paper is intended for research purposes only owing the retrospective nature of the study. It uses DVHs provided by the co-author S.K from the cancer center of Sétif.

***Competing interests*:** The authors have no relevant financial or non-financial interests to disclose.

***Conflicts of interests*:** Declared none.

***Author Contribution*:** (N.D) and (Z.C) contributed equally in this work. (S.K) provided the DVHs.

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