World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Prostate Cancer Volumetric Arc Therapy (VMAT) Analysis

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World Journal of Advanced Research and Reviews, 2023, 19(01), 1033–1044

Publication history: Received on 04 June 2023; revised on 11 July 2023; accepted on 13 July 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.19.1.1311

Abstract

Aim: The purpose of this study was to derive radiobiological parameters from the dose volume histogram of patients that undergone prostate cancer radiotherapy via the VMAT technique.

Material and Methods: A total of twenty-two cases of prostate cancer of 70.2 and 81 Gy were selected for this study. Radiobiological parameters were evaluated by the Poisson equation for the tumor and LKB model for organs at risk.

Results: For prostate tumor, the average TCP was 96.28, 86.45, 68.57 for α/β of 1.2, 3.0, and 10, respectively. The average EUD was 37.98 Gy, 59.23 Gy, 21.19 Gy, 20.65 Gy, 16.32 Gy, and 21.87 Gy for bladder, rectum, right femoral head, left femoral head, small bowel, and large bowel respectively. The average NTCP was 7.6 % for the rectum and negligible for other organs at risk.

Conclusion: NTCP for critical organs and TCP for prostate cancer can be determined via dose volume histogram.

Keywords: Equivalent uniform dose; Normal tissue complication probability; Prostate cancer; VMAT; Tumor control probability

1 Introduction

Apart from non-melanoma skin cancer, prostate cancer has become frequent among men in the United States. This year, an estimated 174,650 men will be diagnosed with prostate cancer [1] with 60% of cases in men over 65 years. Radiation therapy is commonly used to treat prostate cancer but is confronted with challenges due to the proximity of vital organs such as bladder and rectum. Its aim is to maximize the tumor control probability (TCP) with minimum complication to normal tissues in the vicinity through different treatment techniques that included volumetric modulated arc therapy (VMAT).

Recently, VMAT has become customary in prostate treatment as supported by data from multiple institutions [2-4]. Some reports advocated that VMAT will result in lower normal tissue complication probability (NTCP) without compromising TCP compared to the intensity modulated radiotherapy treatment (IMRT) [5-7]. It is a new form of a delivery system that combines gantry rotation speed, dose rate, and multi-leaf collimator. The advantages of VMAT reside in reduced treatment delivery time and improved homogeneity, for example in head and neck tumors [8], and prostate. In addition, VMAT yields a steeper dose fall-off gradients than IMRT [9]. However, the dose escalation is limited by normal tissues toxicities where the rectum is subject to late toxicity after prostate cancer radiotherapy [10,11]. These findings were reiterated by Hardcastle et al. [12] and showed that VMAT reduces dose to the rectum. Also, some reports have recommended that dose escalation in the order of 81 Gy or 70.2 Gy for prostate and prostate bed, respectively, will lead to a greater TCP suggesting a strong dose-effect relationship. To this end, maintaining radiation dose to the planning target volume (PTV) with minimum spillage of radiation dose outside the target is essential to the radiotherapy treatment planning. Thus, the optimization and prediction of treatment protocols through radiobiological

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models are crucial to evaluate treatment outcome. Therefore, the application of radiobiological models will aid in finding the ideal treatment method by assessing and ranking treatment plans.

Usually, the benefit occurs when the physical dose distribution and dose volume histogram (DVH) results are very close and arduous to distinguish. These models have the ability to explain dosimetric differences with tissues reactions by describing their effects through normal tissue responses. They are characterized by equivalent uniform dose (EUD), NTCP, and TCP. The objective of this study was to investigate the radiobiological impact of VMAT on prostate cancer treatment by evaluating the EUD, NTCP, and TCP.

2 Material and methods

A cohort of 22 patients was utilized for this study. The prescribed doses were 81 and 70.2 Gy, delivered in 45 and 39 fractions, for prostate and prostate-bed, respectively. The prescription dose must cover at least 95% of the volume of the PTV, with less than 110% hotspot of the prescribed dose. Patient's age ranged from 41 to 73 years with a median age of 54 years. Patients were immobilized in a Vac-Lok system (CIVCO Medical Solutions, Kalona, Iowa) and computed tomography (CT) scans were acquired with 512 × 512 pixels a t2.5 mm slice using General Electric light speed CT scanner (GE Healthcare, Milwaukee, WI, USA). The slices were selected from the upper border of the L-4 vertebral body to 3 cm below the level of lesser trochanter of the femur. The CT data were imported for contouring in the treatment planning system (TPS) workstation. The dose volume constraints for the target and critical organs for the inverse planning are given in Table 1.

2.1 Radiobiological modeling

Dose-volume histograms (DVHs) in tabular format were extracted for all plans and analyzed with the Biosuite software [5] to derive EUD, NTCP, and TCP. Then, Lyman-Kutcher- Burman (LKB) [13,14] models were applied at the organ at risk (OARs) to estimate EUD and NTCP with variable α/β ratio. The parameters in the calculation are listed in Table 2.

Using the differential DVH (dDVH) of a given dose distribution, the EUD is given by:

$$\mathrm{EUD} = (\Sigma_i^N V_i D_i^a)^{\frac{1}{a}} \quad (1)$$

where N is the number of elements in the dDVH, v_i is the fractional organ volume receiving a dose D_i and a (-10) is a tissue-specific parameter that describes the volume effect.

In this study, Poisson statistics and the linear quadratic (LQ) model were used to determine TCP for prostate plans. The model postulated that cell survival from radiation dose (D_i) in independent subvolume (v_i) obeys Poisson distribution. In this analysis, no correction for overall treatment time nor the effective tumor cell repopulation rate was applied to the TCP calculations. The TCP was calculated for each plan with variable α/β ratio (10; 3; 1.2). Other assumptions such as α = 0.301 Gy^{-1}, αspread =0.114, homogeneous clonogenic cell density =10^7 cells/cm^3, repopulation constant = 0, and delay before repopulation (45 days) were used.

TCP is described by:

$$\mathrm{TCP} = e^{-KS} \quad (2)$$

where K is the tumor clonogen cell number and S the average survival fraction given by $S = \sum_i^N v_i S(D_i)$ (3)

Here in this study, we will refer to TCPP for TCP based Poisson statistics and TCPE as TCP derived from EUD.

2.2 Statistical analysis

Both Levene's and ANOVA test were used for the variance analysis through statistical software Minitab Trial Version 18 (Minitab, State College, PA, USA). The differences were considered statistically significant at $p < 0.05$.

3 Results

Figure 1 illustrates the isodose lines and DVH attained for a patient treated with two arcs arrangements and showing sufficient modulation. The EUD for the selected OARs is depicted in Figure 2. Key parameters of the selected OARs, such

as the volume, EUD, and NTCP distributions were investigated and listed in Table 3. There was no discernible dosimetric difference between the patients for all OARs NTCP except for the rectum. Furthermore, the wide range of SD (± 113.44 cc) observed in the bladder volume, showed the variability of maintaining adequate filling during treatment. It was also found in Table 3 that the NTCP values for rectal bleeding and stricture range from 3.0% to 10.5% with a mean value of 7.65 ± 2.09 %. The dependencies of rectal EUD, NTCP, and volume are illustrated in Figure 3. There was a nonsignificant correlation between rectal volume and NTCP (R^2=0.068; p<0.05) in one hand, and EUD (R^2=0.065; p<0.05) in the other hand. However, a good correlation was found between EUD and NTCP with a regression coefficient of R^2= 0.844 (Figure 4). These findings between volume, NTCP, and EUD of the rectum are condensed as a 3D surface plot in Figure 5. In this report, the mean prostate volume was estimated at 83.09 ± 62.68 cc with a coefficient of variation (CV) in the order of 0.754 suggesting a 75.4% dispersion.

Table 1 Dose-volume constraints recommendations for target volume and organs at risk in prostate cancer radiotherapy

Target Volume (PTV)	D_{min}>90% The minimum dose for PTV must be higher than 90% of the prescribed dose. V_{95}>95% The volume receiving at least 95% of the prescribed dose must be higher than 90% of the total volume
Bladder	V_{65}<50% V_{70}<35% V_{75}<25% V_{80}<15%
Rectum	V_{50}<50% V_{40}<35% V65<17.5% V80<15%
Femoral Head	Dmax=60 Gy V_{50}<10% V_{40}<45%
Bowel	Large D_{max} = 55Gy Small D_{max}=55 Gy V45< 195 cc V30< 300 cc

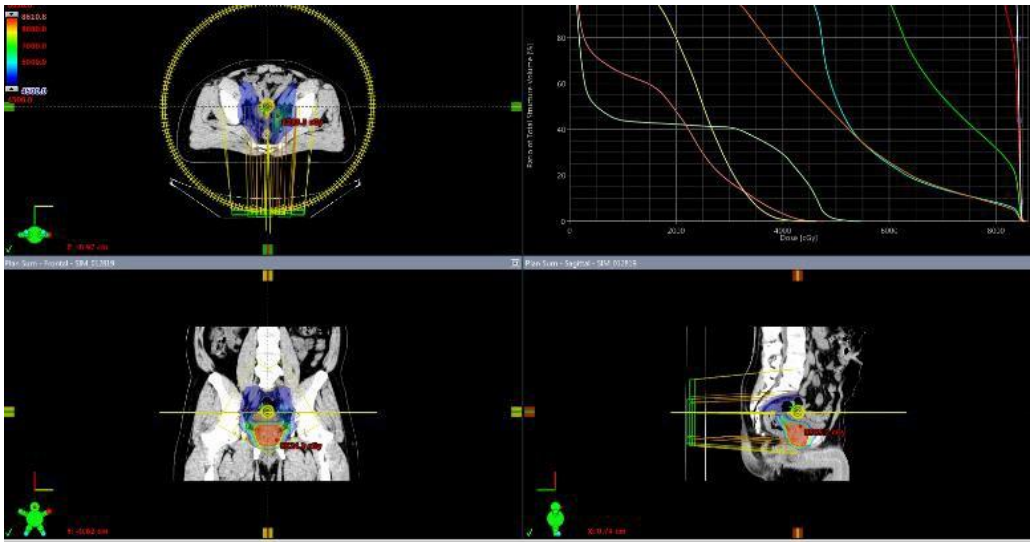

Figure 1 Isodose and DVH for one patient treated with two arcs using VMAT

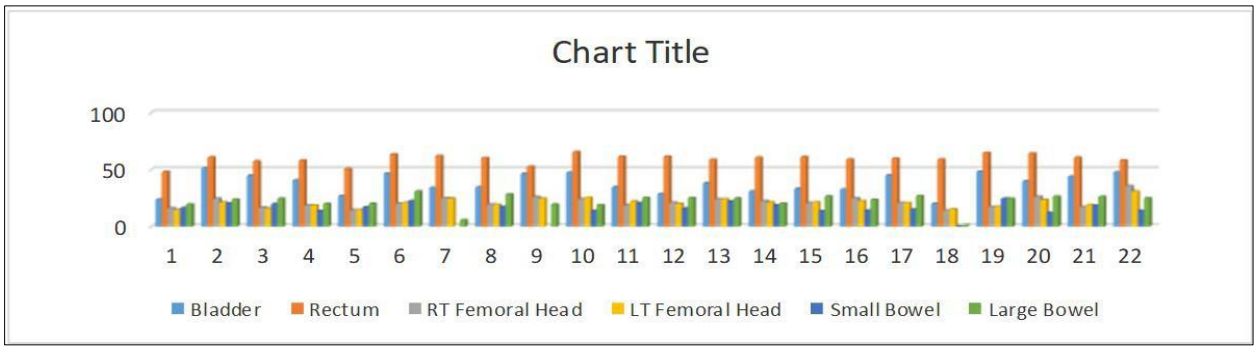

Figure 2 Equivalent uniform dose (EUD) of the selected OARs in this study

Table 2 Biological parameters, n, m, and TD50 used for the NTCP calculation

Organ	M slope	N volume effect	TD_{50} (cGy)	Endpoint
Bladder	0.11	0.5	80	Contracture
Rectum	0.27	0.085	97.7	Stricture-Bleeding
Femoral head	0.12	0.25	65	Necrosis
Bowel	0.16	0.15	55	Obstruction-Perforation

Table 3 Results of radiobiological values obtained for organs at risk

Organ		Volume (cc	EUD (Gy)	NTCP (%)
Bladder		233.29 ±113.44	37.98±8.77	0.00
Rectum		67.80 ± 29.67	59.23±4.27	7.65±2.09
Femoral head	Left	94.28±48.96	21.19±4.88	0.00
	Right	94.23±48.55	20.66±3.95	0.00
Bowel	Small	921.73±814.45	16.32±5.17	0.00
	Large	311.55±302.53	21.87±6.83	0.00

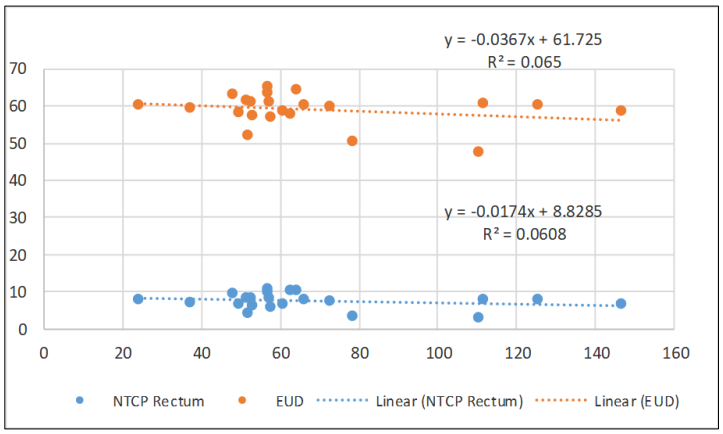

Figure 3 Linear regression correlation between Volume and EUD (a) and NTCP (b) for prostate patient treated with VMAT

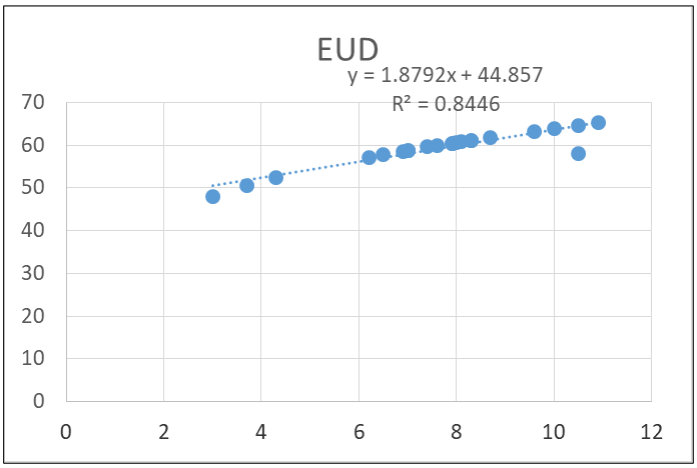

Figure 4 Linear regression correlation between EUD and NTCP of the rectum

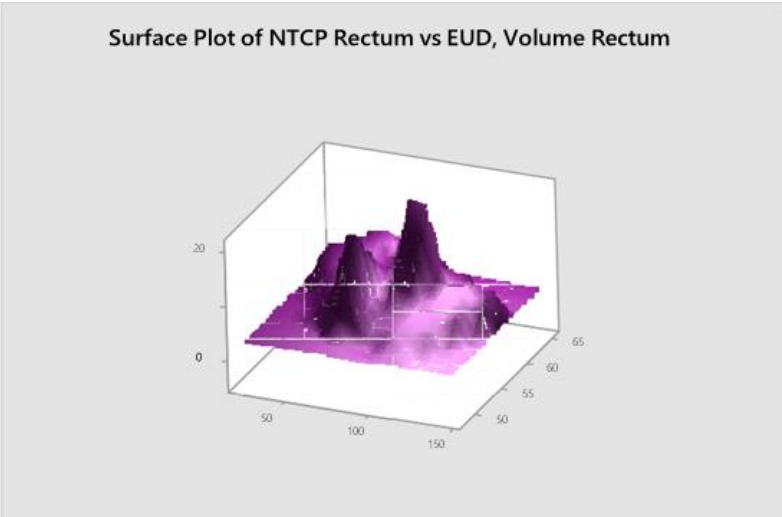

Figure 5 A summary of relationship between volume, EUD, and NTCP of the rectum during prostate irradiation

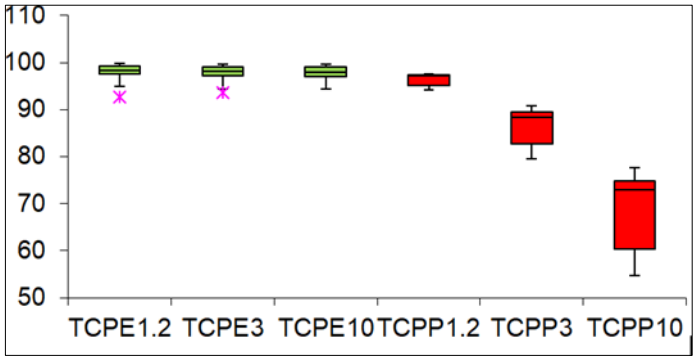

Figure 6 Box-and-whisker plots of tumor control probability (TCP) values obtained with EUD based TCP model (green) and Poisson statistics (red) for variable α/β ratio

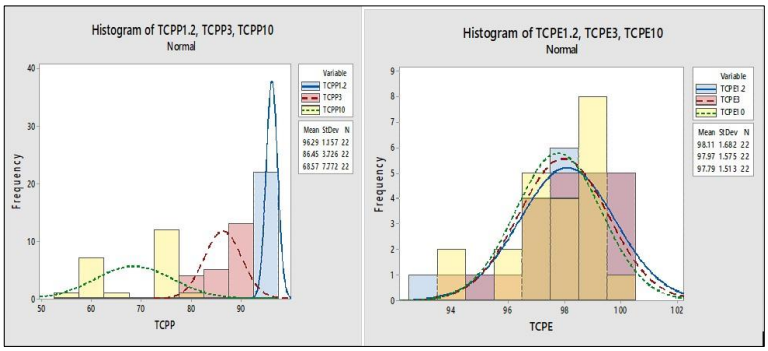

Figure 7 Density Plot of TCP based Poisson (a) and EUD model (b) for variable α/β ratio

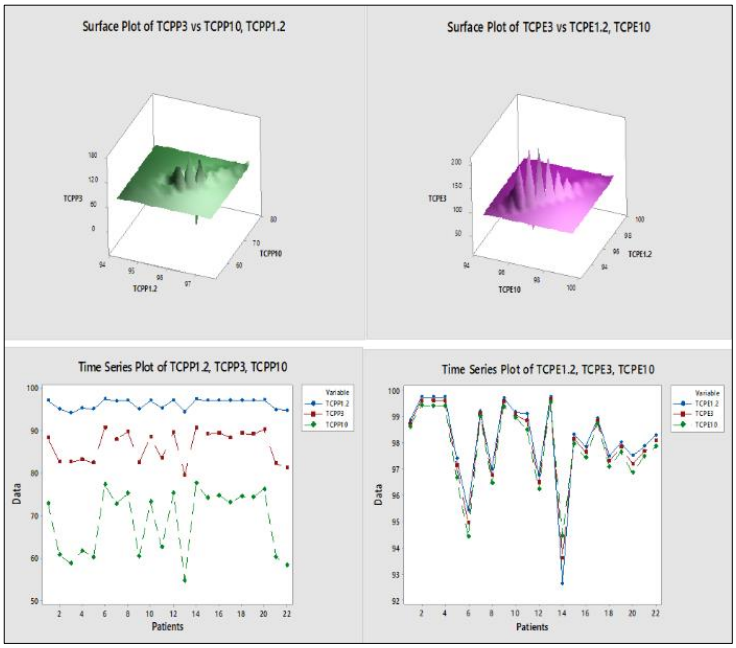

Figure 8 Surface plot (top) and time series plot (bottom) of TCP based Poisson (a) and EUD model (b) for variable α/β ratio

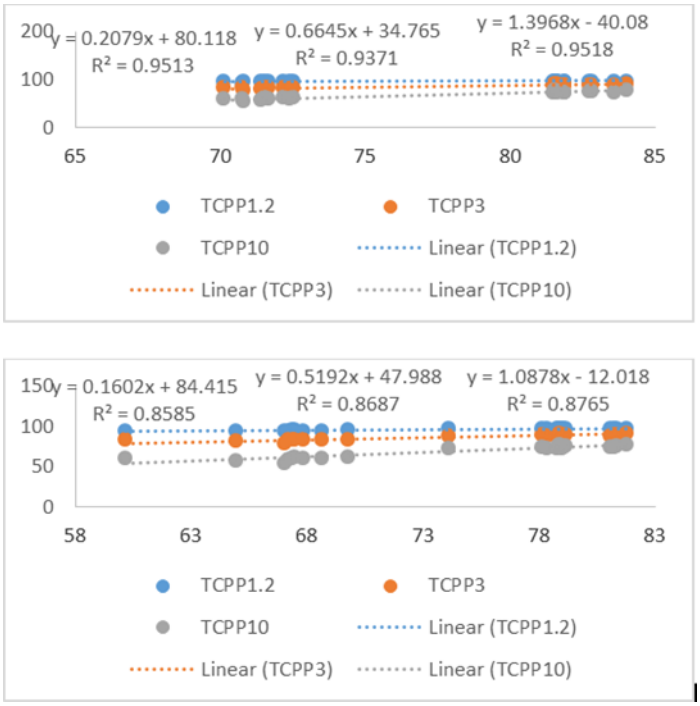

Figure 9 Linear regression correlation between TCP (Poisson model) and D95% (top), and D_{min} (bottom) for variable α/β ratio

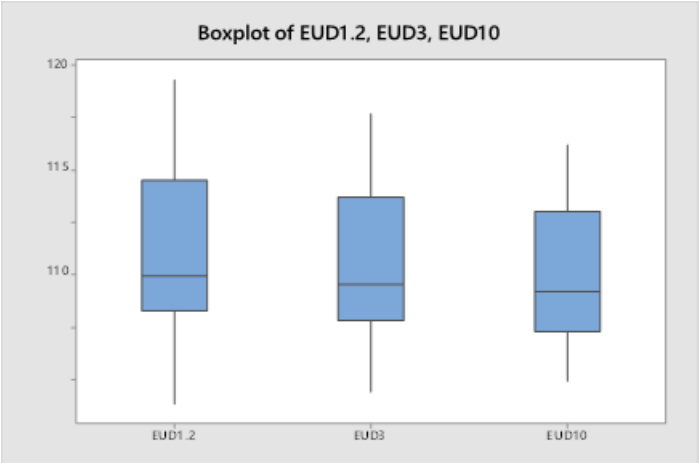

Figure 10 Graphical presentation of equivalent uniform dose (EUD) for VMAT plans for α/β ratio of 1.2, 3.0, and 10, respectively. Horizontal line = mean value; box = 95% confidence interval; whiskers = maximum and minimum values.

Figure 6 illustrated a whisker box plot of TCP irrespective of the models. TCPE was associated with significantly higher TCP compared to TCPP for all three α/β ratios (p< 0.005 in each case). The lower α/β ratio results in a greater gain for TCP from the two methods. Table 2 listed the mean and standard deviation values of the calculated TCP. Furthermore, the variability of both models was assessed through Levene's and ANOVA test. The null hypothesis (H_0) stated that the standard deviations within each TCP defined by α/β ratio are the same.

Since the P-value of the F-test is less than 0.05, there is a statistically significant difference between the means of the TCP. In contrast, both Levene's (0.9998) and ANOVA (F-ratio = 0.219682) revealed a P-value ≥ 0.05 in the TCPE. Consequently, there is not a statistically significant difference between the means for variables α/β ratio at 5% significance level.

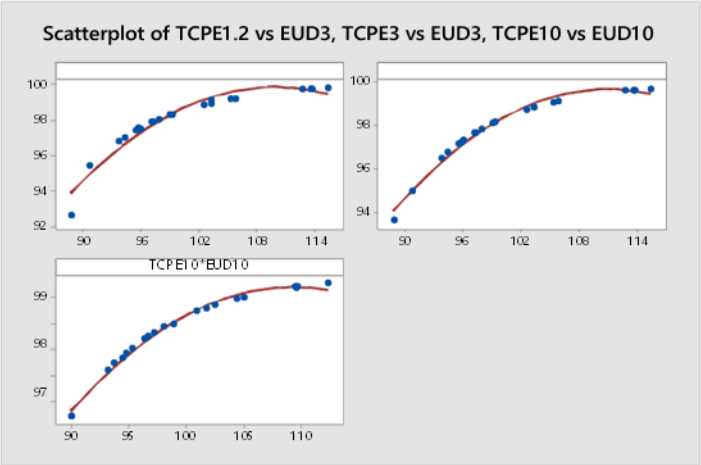

Figure 11 Dependence of EUD with TCP EUD based model (TCPE). The quadratic regression coefficient R^2 =0.973, 0.9646, and 0.9809 for α/β ratio of 1.2, 3.0, and 10.0, respectively**.**

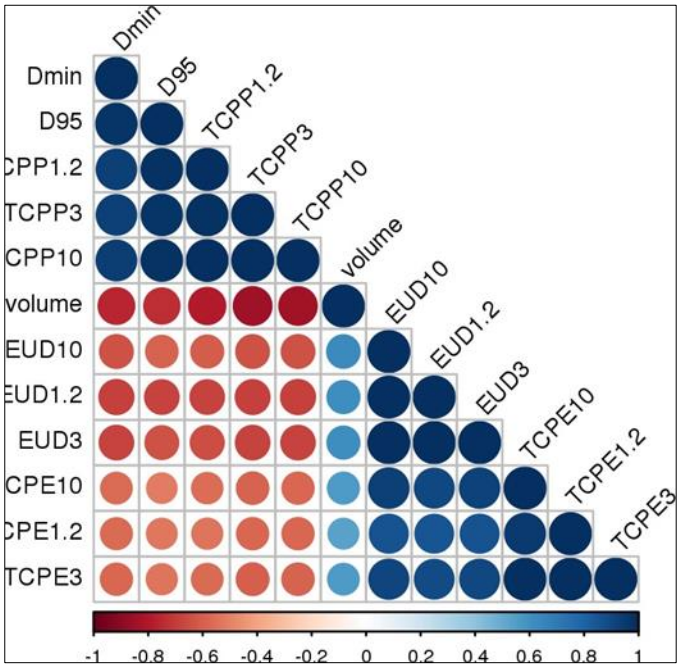

Figure 12 The cross-correlation matrixes for the variables belonging to 22 patients treated with VMAT for prostate cancer. The color bar represents the Spearman's rank correlation coefficient value.

Figure 7 shows the density distribution of TCP calculated using both methods for variable α/β ratio. A clear deviation from normality was seen with TCPP irrespective of α/β ratio. The results are presented in Table 5 using Anderson Darling test. The test rejects the hypothesis of normality when the p-value is less than or equal to 0.05. In TCPP, with 95% confidence, the data does not fit the normal distribution. In contrast, the p-value is ≥0.05 with TCPE, implying that the data do not follow a normal distribution.

Figure 8 summarized the TCP evaluation results for prostate cancer derived from both models. A general trend of TCP distribution emerged from patients to patients and from α/β ratio. A clear difference between TCPP patient for variable α/β ratio is noticeable on the time series plot. In contrast, there is no clear difference in the patterns exhibited by TCPE patients for variable α/β ratio. The P-value (0.0000) is less than 0.05 in the TCPP, suggesting that there is a statistically significant difference amongst the standard deviations at the 95.0% confidence level. Similar results were found using the ANOVA test with F-ratio equals 172.261.

Figure 9 illustrated the correlation between TCPP and DVH physical indices such as $D_{95\%}$ and D_{min} through Spearman's test. It revealed that all TCPPs are significantly associated with D95% and D_{min} regardless of α/β ratio as indicated in

Table 6. A better correlation coefficient was observed with $D_{95\%}$ compared to D_{min}. The EUD of prostate VMAT plans for variable sensitivity is illustrated in Figure 10.

The inter and intra-variability of EUD was assessed using ANOVA test with F-ratio is equals to 0.703 implying that there is not a statistically significant difference between the means at the 5% significance level since the P-value ≥ 0.05. Furthermore, the relationship between EUD and TCP for the corresponding/β ratio was examined by fitting the data through a quadratic equation. Figure 11 exhibited the dependence of the EUD and TCP and showed that TCP increases sigmoidally with increasing EUD irrespective of α/β ratio. The regression gets better as α/β ratio increases (α/β=1.2 R^2=0.9373; α/β=3.0 R^2=0.9649; α/β=10.0 R^2=0.9809). All calculated data for prostate tumor that include EUD, TCPP, TCPE, $D_{95\%}$, D_{min}, and volume were combined and examined through a cross correlation matrix (Figure 12) using the Spearman's rank test. The color bar represents the Spearman's rank correlation coefficient value.

4 Discussion

This study investigated 22 prostate cancers cases through the lenses of radiobiological parameters such as EUD, NTCP, and TCP that were well established [6,15] to characterize treatment plans. We reported on NTCP values of the bladder, femoral head, and bowel close to 0.0% like that observed by both Vlachaki et al and Luxton et al. [16,17]. The large standard deviation (±113.44 cc) seen in bladder volume in our study, suggests a higher degree of variability for bladder filling. Waddle et al. [18] analyzed data from several patients and indicated the age to be a potential factor. It was also revealed that more than 30% of patients with high-risk prostate cancer have prior bladder issues which makes the underlying toxicity difficult to assess [19]. Harsolia et al. [20] contended that an initial bladder wall volume is more associated with chronic genitourinary toxicity than the absolute solid volume of the bladder. For the rectum, there is no standard volume definition for DVH comparison. A study carried out by Geinitz et al. [21] on different rectal contours uncovered that a uniform rectal volume definition is warranted and would lead to more comparable DVH results. The same observation was made by Michalski et al. [22] where they found out that an increase in late bowel toxicity correlated well with the treatment planning system (TPS) total rectal volume greater than 100 cm^3. Therefore, accurate rectal volumes characterization is essential during prostate treatment planning. NTCP of the rectum in our study was 7.6±2.09%. It was determined through contouring but correlated poorly (R^2= 0.0608) with the rectum volume. In fact, it was higher compared to that of Rana et al. [23] 0.01 ± 0.46 %. Other results by Luxton et al. [17] showed that the mean NTCP values for rectum were 1.7% for IMRT vs. 3.2% for 3DCRT. The findings were later corroborated by Vlachaki et al. [16]. Several data from the literature cited that NTCP with a rectal bleeding endpoint is associated with different rectal contours. As a result, when applying dose constraints to the rectum, contouring becomes a significant factor that determines the risk of rectal toxicity. It is well established that rectum DVH fluctuates significantly due to daily anatomic changes and setup variations [24,25]. Consequently, rectal NTCP interpretation requires careful attention as confounding factors may impact its analysis in addition to the anatomy. Further, some parts such as anterior rectal wall may lead to increased risk as the prostate get irradiated. The rectum EUD (59.23 ± 4.27 Gy) in our report was higher than that of Khuntia et al. [26] where they showed that an acute rectal toxicity was not seen with rectal EUD values of 46.78 Gy. However, our results agreed with those of Mesbahi et al. [27] in which 10 patients with prostate adenocarcinoma were evaluated using the LKB model. Similar results were found by Cambria et al. [28]. In their case, the rectum NTCP correlated well to clinical complications of late rectal toxicity and divulged a link between the toxicity rate evaluated based on the LKB model and clinical outcome. NTCP calculation is influenced by the input parameters, m and n. m is described as the sigmoid curve steepness, and n as the magnitude of the volume effect. As n decreases or m increases, higher rectum NTCP will ensue.

The TCP calculations were performed using Poisson statistics and the EUD based-TCP model with variable α/β ratio. Our report showed the TCP dependence on α/β ratio variations with Poisson model to be comparable to that of Deb et al. [29] using Kallman S-model. It was revealed in our study that lower α/β ratio results in higher TCP using Poisson model, as echoed by Fowler et al. [30-32]. Our TCPP (86.45±3.72) for α/β=3, is comparable to that of Fu et al. [33] where they reported a TCP of 86.35%, bladder NTCP of 0.00%, and rectum NTCP of 7.59% for IMRT prostate treatments. In contrast, TCPE varies little with change in the prescribed dose (prostate bed treated at 70.2 Gy and prostate at 81 Gy) or variation in the α/β ratio. The modifications were statistically insignificant and similar results were detected with EUD.

In the current analysis, DVH was utilized to calculate potential treatment plans predictors. The choice of the optimization strategy in those predictors is very important as it will impact patient treatment outcome. Some reports advocated in general, EUD-based plans because they proposed better OAR sparing when compared to LKB-based plans. This is due to EUD-based cost functions that are degenerative in nature and have the tendency to find the optimal solution [34]. Our study is not exhaustive because of limitations due to its scope. The small number of plans examined in this report could be considered as representative of a patient population with prostate tumors. This is coupled with

the parameters used in these models for a range of α/β ratio. The predictors are calculated based on DVH reduction scheme that should safeguard the complication probability while changing DVH profile to a parameter. DVH as a lone quantifier has been challenged by several reports because of the loss of positional and organ-specific spatial information in the volume and ignore the fraction size variations. A combination of DVH, 3D doses, and organ functional maps is essential to overcome these limitations. The use of dose surface maps (DSM) for example on the rectal wall allows the integrity of geometric information during dose accumulation thus, compensating a limitation linked to DVH. Rectal toxicity prediction can be improved by incorporating parameters of delivered DSM into NTCP modeling [35]. Alfonso et al. [36] proposed the concept of dose distribution index (DDI) where key dosimetric parameters such as dose coverage, conformity, and homogeneity indices over the PTV, as well as sparing indices of the OARs could be incorporated into the calculation system. Of equal importance, some studies have attempted to establish the age effect as a part of general NTCP model, especially with larger datasets. Finally, the use of smaller radiation fields would probably lessen the occurrence of secondary rectal cancers due to a smaller volume of the rectum in the radiation field of view (FOV). These factors are more helpful in developing a risk "free" approach during prostate radiotherapy.

The study did not consider inter-or intra-fractional positioning variability of the patient nor the precision of VMAT. In a Monte- Carlo simulation, Balderson et al. [37] used a systematic shift of 15mm both directly and between static gantry IMRT fields. They showed that the mean TCP to be between 96% and 98%, whereas on VMAT plans, change in mean TCP values is between 45% and 74% signifying the unforgiveness of geometric miss errors of VMAT compared to IMRT. However, we were aided in our study with cone beam computed tomography (CBCT) and a margin put on the prostate. The use of TCP, NTCP, and EUD as a predictive model is still contested. These parameters depend on the LQ model. For high dose, the LQ model overvalues cell killing process, consequently, overestimates NTCP [38]. Due to significant variation between delivered and prescribed doses, EUD, NTCP, and TCP should be employed as a predictor.

5 Conclusion

Prostate VMAT plans with two arcs arrangements were used in our study. The DVH was used to calculate the radiobiological parameters via different models. The data produced EUD, NTCP for all OARs selected and TCP for prostate tumor. The study revealed that these values are valuable for treatment plans comparison and a complementary tool for assessing toxicity risk.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to disclosed.

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