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# Risks of Radiation-Induced Secondary Cancer: Prostate Volumetric Arc Therapy (VMAT)

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## ARTICLE INFORMATION

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## ABSTRACT

Risks of radiation-induced cancer for 11 patients following prostate radiotherapy with Volumetric Modulated Arc Therapy (VMAT) were investigated. Prostate plans called for 81 Gy in 45 fractions using 10 MV photon beam. Dose volume histograms from pelvic CT scans were extracted to compute Organ Equivalent Doses (OED) and Excess Absolute Risks (EAR) of bladder and rectum, using bell-shaped and plateau models. EARs were calculated for patients irradiated at age 40 and attained at age 75 years. EARs for the rectum were  $7.037 \pm 0.222$  Gy and  $8.894 \pm 0.248$  Gy per 10,000 persons per year (PY) for bell-shaped and plateau model, respectively. EARs for the bladder were  $0.696 \pm 0.500$  Gy and  $1.758 \pm 0.0181$  Gy per 10,000 persons per year for the bell-shaped and plateau model, respectively. Calculated EAR of the bladder resulted in the lowest risks compared to the rectum using both bell-shaped and plateau model.

**Key words:** Excess absolute risks, organ equivalent dose, CT scans, plateau models, bladder

## INTRODUCTION

Prostate cancer is the second most common malignancy diagnosed in men today. In fact, it is the fifth leading cause of cancer-related death worldwide<sup>1</sup>. Several options, including diverse forms of surgery and Radiation Therapy (RT), are considered for patients with localized prostate cancer. However, the occurrence of secondary cancers as an unintended consequence of RT is not well understood. Recently, the organs at risk (OAR) in the vicinity, such as bladder and rectum, have been identified as common locations for secondary cancers in these days. The causes are currently under investigation. Several lines of research are trying to quantify the risk of Second Primary Cancers (SPC) in prostate cancer patients receiving RT compared to patients receiving other forms of treatment.

Chun<sup>2</sup> investigated the risk of bladder SPC induction after RT and demonstrated an increase in the relative risk for primary cancer incidence, regardless of the treatment modality used for prostate cancer irradiation.

Moon *et al.*<sup>3</sup> reported a higher rate (5.6 vs 3.7%) of bladder cancer for patients who underwent prostate radiation therapy compared to surgery and observation, based on epidemiological data.

Baxter *et al.*<sup>4</sup> found a significant increase in the development of rectal cancer after prostate irradiation and showed a specific direct link to the irradiated tissue.

Wachter *et al.*<sup>5</sup> showed that even at a reasonably low dose, the rectum could be subject to high-risk toxicity after prostate irradiation.

Nieder *et al.*<sup>6</sup> used a hazard ratio to quantify the relative rectal cancer risk after external beam radiotherapy (EBRT). They obtained a value of 1.26, suggesting a possibility of secondary rectal cancer after radiotherapy compared to the background incidence of spontaneous cancers.

Several authors<sup>7,8</sup> calculated dose-effect relationships using the linear, plateau and bell-shaped models in order to investigate Secondary Cancer Risk (SCR) using Organ Equivalent Dose (OED) as a surrogate. They all detect an increasing risk with dose in the linear model. However, they find an exponential decrease of risk with higher dose in the exponential model. Finally, they showed that there could a saturation of risk at high doses for the plateau model. However, which of the three models best describes the elevated risk depends on both the tissues type and the prescribed dose.

The objective of this report was to offer information on the Excess Absolute Risk (EAR) after prostate cancer irradiation. In this study, OED and Excess Absolute Risk (EAR) for the bladder and rectum were estimated, using the bell-shaped and plateau models. The patients in this study who received radiation were treated using the VMAT technique.

### MATERIALS AND METHODS

Eleven Patients with localized prostate cancer were selected for this study. Their ages ranged from 55 to 75 years, with a median of 68 years. The treatment plans called for 81 Gy in 45 fractions using VMAT. Here, the Gross Tumor Volume (GTV) is defined as the whole prostate. The Planning Target Volume (PTV) was defined by expanding the GTV by 6 mm. The rectum, bladder and femoral heads were contoured as organs at risk (OAR). All plans were carried out using the Eclipse® Treatment Planning System (Varian Medical Systems) version 15, using a 2.5 mm grid resolution. Differential dose-volume histograms (DVHs) using 0.01 Gy bin widths for the rectum and bladder were generated for two arcs with 10 MV photon energy. The risks of radiation-induced second primary cancer were examined by quantifying OED and EAR. Table 1 lists the OAR dose constraints applied in this study.

**Modeling risk of radiation-induced cancer:** This study uses the concept of OED, developed by Schneider and Kaser-Hotz<sup>9</sup>, to evaluate Secondary Cancer Risk (SCR). This metric can be applied to several different models of the cell kinetics for radiation-induced cancer, reflecting different underlying

Table 1: Dose constraints for bladder and rectum

OARs	Constraints
Bladder	V80 ≤ 15%
	V75 ≤ 25%
	V70 ≤ 30%
Rectum	V65 ≤ 50%
	V50 ≤ 15%
	V70 ≤ 20%
	V65 ≤ 35%
	V50 ≤ 50%

Table 2: Parameters used in OED calculation for the bell-shaped and plateau models. All models use the ratio α/β = 3

	Plateau	Bell
	-----	-----
OARs	α	α
Bladder	0.633	0.213
Rectum	0.065	0.031

processes for the dose-response relationship<sup>10,11</sup>. In this paper considered the bell-shaped dose-response model and the plateau dose-response model. Specifically, given a dose-response model, OED is then calculated from an inhomogeneous dose distribution using data from the DVH. The OED for a bell-shaped dose-response model was determined as follows:

$$OED = \frac{1}{V_T} \sum_i V_i \cdot D_i e^{-\alpha \cdot D_i} \quad (1)$$

The OED for a plateau dose-response model was determined as follows:

$$OED = \frac{1}{V_T} \sum_i V_i \cdot \frac{1 - \exp(-\delta \cdot D_i)}{\delta} \quad (2)$$

The parameters of the models were based on the constants α and β, which were the cell kill parameters of the linear quadratic model. δ is an organ-specific dose response parameter calculated from α and β.

In this study,  $\delta = \alpha + \beta D \frac{d}{DT}$  and α/β was set at 3 for bladder and rectum. D<sub>T</sub> represents the prescribed dose of 81 Gy to the target volume, d is the dose per fraction and D is the dose absorbed by the organ under consideration. The parameters used in the OED calculation for the bell-shaped and plateau models are given in Table 2 and taken from Schneider *et al.*<sup>12</sup>.

**The Excess Absolute Risk (EAR):** In this report used the Biological Effects of Ionizing Radiation (BEIR) VII<sup>13</sup> report to estimate the risks of solid secondary cancer in the bladder and

rectum for patients aged 40 to 80 years old. EAR is defined as the difference in cancer rates attributable to radiation and age. It is evaluated using the OED as follows:

$$EAR = \frac{1}{V_T} \sum_i V(D_i) \times \beta \times OED(D_i) \times \mu(\text{age}X, \text{age}A) \quad (3)$$

The age-modifying function  $\mu$  is given by

$$\mu(\text{agex}, \text{agea}) = \exp \left[ \gamma_e (\text{age} - 30) + \gamma_a \ln \left( \frac{\text{agea}}{70} \right) \right] \quad (4)$$

where, the parameters  $\gamma_e$  and  $\gamma_a$  are gender-averaged and centered on an age at exposure of 40 years and an attained age of 75 years. Table 3 displays all the dose-response parameters used in the EAR calculation<sup>9</sup>.

Table 3: Schneider's best-fit parameters for the various dose-response models

OARs	Bell shaped model $\alpha$ (Gy <sup>-1</sup> )	Plateau model $\alpha$ (Gy <sup>-1</sup> )	$\beta^a$		
			For calculation of EAR for all models mentioned		
Rectum	0.031	0.065	0.73	-0.056	6.90
Bladder	0.213	0.633	3.80	-0.024	2.38

**Statistical analysis:** Statistical analysis was carried out using Minitab 18 (Minitab, LLC, State College PA, USA) for descriptive statistics. Differential dose volume histogram (DVHs) were extracted from the Treatment Planning System (TPS) and used to calculate OED and EAR. Student's t-test and the nonparametric Wilcoxon signed-rank test were used to compare paired samples. A p-value <0.05 was considered statistically significant. To determine interrelationships between patients EARs and dosimetric parameters, a Principal Component Analysis (PCA) and hierarchical clustering analysis were performed.

## RESULTS

All treatment plans showed that 99% or more of the PTV received at least 81 Gy. The dose distributions for the VMAT treatment plans are illustrated in Fig. 1. The cumulative DVHs in the bladder and rectum for one patient are shown in Fig. 2. The means and standard deviations of the dose received by the OARs under consideration are  $36.20 \pm 8.65$  Gy for bladder and  $35.58 \pm 7.16$  Gy for rectum, across all 11 prostate cancer patients. The mean EARs for

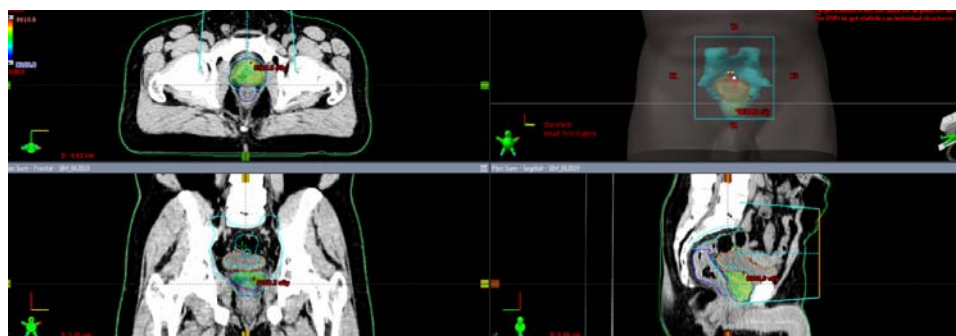


Fig. 1: Dose volume histogram for prostate tumor treated with VMAT (81 Gy) irradiation

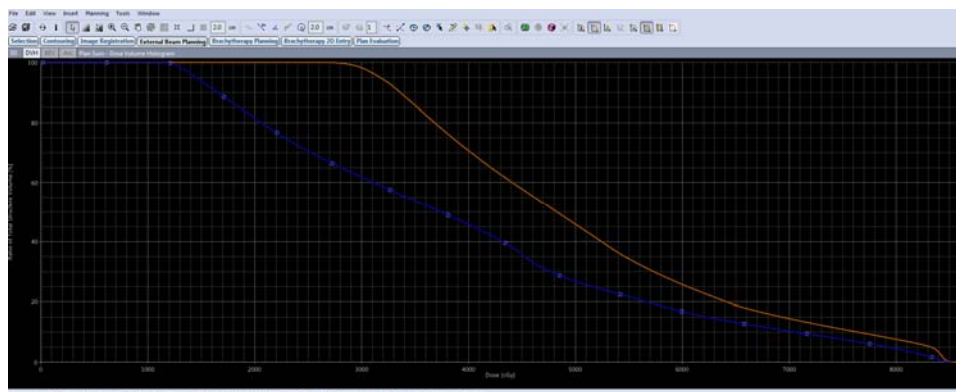


Fig. 2: OAR dose volume histogram: Rectum (blue) and the bladder (orange)

organs partially included in the treatment field during prostate radiotherapy are presented in Table 4, for both models. The EAR values calculated for the rectum are considerably higher than those calculated for the bladder, because the former is closer to the target volume. The mean and standard deviation of EAR values for the bladder are  $1.568 \pm 2.357$  Gy and  $1.758 \pm 0.018$  Gy for the bell-shaped and plateau models respectively. The mean and standard deviation of EAR values for the rectum are  $7.037 \pm 0.222$  Gy and  $8.894 \pm 0.248$  Gy for

the bell-shaped and plateau models respectively. Figure 3a and 3b present the various dose-effect models of EAR for the rectum and bladder.

Figure 4 depicts cross-correlation matrices between excess absolute risk and dosimetric variables. Both strong negative and strong positive correlations are observed in the data. Figure 5a and 5b display the available clinical variables and treatment characteristics of the bladder and rectum for each patient. The dendrograms adjacent to the matrix axes show the results of a clustering analysis on the patients (vertical axis) or variables (horizontal axis).

Finally, a one-way analysis of variance was conducted to compare the effects of the model on the estimated EAR. This analysis revealed statistically significant differences between

Table 4: Mean and SD of EAR among all patients, for bladder and rectum using the bell-shaped and plateau models

Organ	Bell-shaped	Plateau
Bladder	$0.696 \pm 0.500$	$1.758 \pm 0.0181$
Rectum	$7.037 \pm 0.222$	$8.894 \pm 0.248$

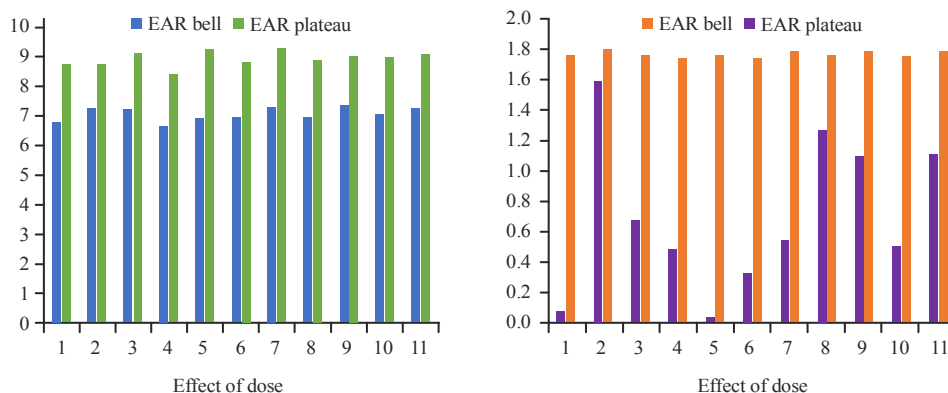


Fig. 3(a,b): Present the various dose effect models on EAR for the (a) Rectum and (b) Bladder

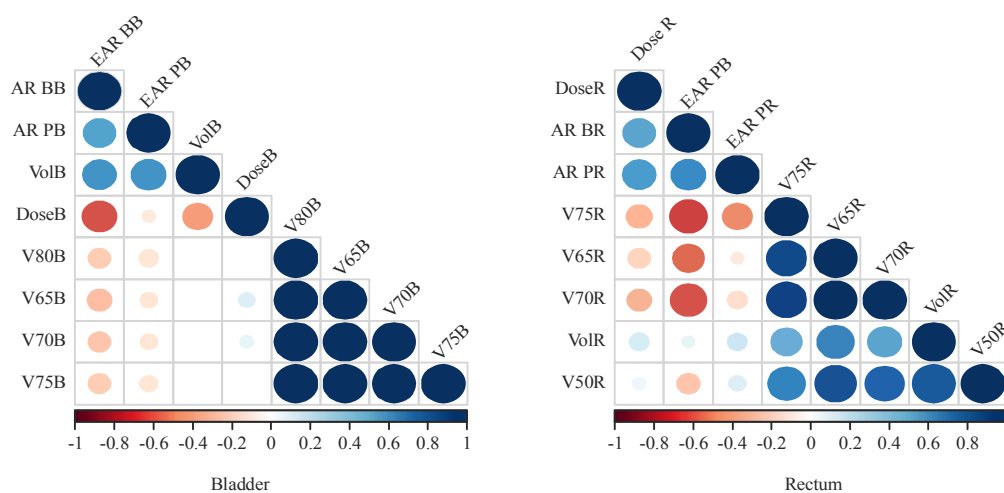


Fig. 4: Cross-correlation matrices showing the interactions among 4 functional secondary cancer risks and dosimetric parameters. The color scale and marker size both represent Pearson's correlation coefficient. Correlations are only displayed if the correlation test p-value is >0.05

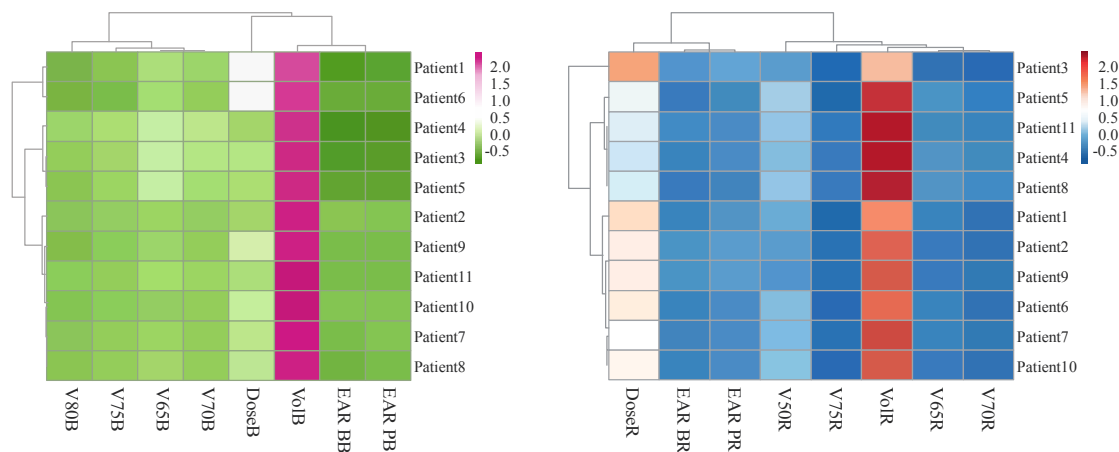


Fig. 5: Heat maps of excess absolute risks calculated using the bell-shaped (EARBB) and plateau (EAR PB) models, along with various dose constraint parameters. The left-hand plot shows results for the bladder and the right-hand plot shows results for the rectum. The hierarchical clustering of patients and variables (dendrograms) were generated using Spearman correlation coefficients. The color scale indicates the degree of correlation (z-Scores)

the mean bladder EAR values calculated under bell-shaped and Plateau models, as determined by  $F(2,20) = 49.3856$ ,  $p < 0.05$ . Similarly, there were statistically significant differences between the mean rectum EAR values of the two models, with  $F(2,20) = 341.864$ ,  $p < 0.05$ .

Here used Hierarchical Clustering Analysis (HCA) to discover groups of patients with similar patterns of dosimetric variables and risk measures. This process automatically classifies and groups comparable entities (vectors) into small clusters and subsequently grows the clusters by adding other similar members. The results of HCA are displayed as dendrograms in Fig. 5. Principal Component Analysis (PCA) shows that two components (PC1 and PC2) explain nearly all of the variance among patients. Specifically, PC1 and PC2 explain 98.1 and 1.1% of the variance in bladder variables respectively. In a different PCA analysis for the rectum variables, the first two principal components, PC1 and PC2, explain 95.9 and 3.8% of the total variance respectively. A cross-correlation analysis to determine the relationships between dose constraint parameters and excess absolute risks found both strong negative and strong positive correlations, for both bladder and rectum.

## DISCUSSION

In this study analyzed the risks of radiation-induced secondary cancer for prostate patients treated with a 10 MV photon beam VMAT. Calculated the effect of radiation-induced malignancies on the bladder and rectum using the bell-shaped and plateau models. Also found that the bladder has

a lower risk than the rectum, regardless of the model used to calculate EAR.

Despite the differences in treatment modalities and modeling approaches, these results compare well with those of Raghad *et al.*<sup>14</sup> who evaluated EARs ranging from 1.44-2.69 and 1.70-2.42 per 10 000 persons Per Year (PY), for rectum and bladder respectively, using a mechanistic model.

**Sources of uncertainty:** Jain *et al.*<sup>15</sup> revealed that acute bladder toxicity is highly dependent on bladder filling. Lebesque *et al.*<sup>16</sup> have pointed out that it was difficult to find a strong relationship between dosimetric parameters of the bladder and late complications, for precisely this reason. However, despite widespread recognition that bladder filling poses a problem for treatment, there is no agreement on how to contour the bladder structure in treatment plans.

As for the rectum, the characterization of its volume and length in TPS varies extensively between authors and institutions. For instance, Fiorino *et al.*<sup>17</sup> defined the whole rectum from the anal verge to the rectosigmoid flexure, while others contoured from the anal verge proximally to the sacroiliac joint<sup>18</sup>. They found that the risk of rectal bleeding increased from 10 to 63% when the irradiated rectal volume increased from 25 to 100% suggesting a clear delineation process, variability influenced by the imaging technique and modality used.

Several factors must be accounted for when estimating the risk of cancers from RT. In general, these include the uncertainties associated with the TPS and the risk models. For



example, in EBRT, the doses to OARs lie mostly outside of the treatment field and TPS models usually do not portray these doses because of head scatter and leakage. Monte Carlo modeling can be used instead of standard TPS histograms to account for this limitation.

However, the SCR estimate depends strongly on the choice of model and the RT technique used. Athar *et al.*<sup>19</sup> accentuated the potential of reducing the incidence of SCR by cautiously selecting the RT technique. They associated the combined risk due to secondary radiation effects (scattering) during IMRT delivery with the energy, distance from the target, tissue depth and use of a multileaf collimator. In a chest irradiation study, Sasse *et al.*<sup>20</sup> reported that a decrease in field size leads to a reduced incidence of Second Malignant Neoplasm (SMNs). Similarly, De Bruin *et al.*<sup>21</sup> found a correlation between field size and secondary breast cancer risk. Travis *et al.*<sup>22</sup> and Dores *et al.*<sup>23</sup> demonstrated that reducing RT field size and volume leads to a lower incidence of secondary solid tumors for lung, gastric and esophageal cancer. Hence, all SPC risk models should be used with caution, as their interpretation can be significantly altered by the choice of model. For example, the use of linear models has been shown to overestimate the risk of SPC induction<sup>24,25</sup>.

This dose-response models were used here did not consider several factors, including cell repair, repopulation and spontaneous processes. Their simplicity increases the number of uncertainties involved in the OED and EAR calculations. However, the chief source of cancer risk was still the primary radiation. Here, 10 MV was used for treatment. One would therefore expect a small additional contribution from neutron scattering. This effect was not included in this calculation, because the TPS does not perform neutron transport calculations. We were aided in the treatment by Cone Beam Computed Tomography (CBCT), which minimizes patient motion as well as putting a margin on the target. The imaging dose was also not included in this study. Nevertheless, in the study released by Kim *et al.*<sup>26</sup> the EAR from pelvis scan is higher than that of the head, neck and chest. They indicate that after a 30 CBCT scan for the pelvis, the EAR could approach 400 per 10,000 persons, showing the influx of imaging dose in SCR. Another limitation of this model comes from differences in the beam weighting due to the choice of treatment modality, which can change the dose distribution. For instance, VMAT uses non-uniform beam weighting to prevent a photon entrance dose to the rectum. Further, all the EAR models used in this study were simplified because they were based on the DVH. Parameters such as long latency periods, lifestyle and exposure to smoking were not included in the study.

Finally, the study demonstrates that exploratory PCA can be used to assess the links between dosimetric parameters of OARs and EARs within an organ and between patients. This approach can be used to tailor personalized radiotherapy treatments.

## CONCLUSIONS

Several studies have used the bell-shaped and plateau models to evaluate SCR via the dose-response relationship. It is widely agreed that such SCR estimates can be used to rank and optimize treatment plans based on OAR dose. All SCR calculations are prone to large uncertainties from a variety of sources such as those listed above, so absolute risk should be interpreted with reluctance. However, using such models for relative comparisons, for example to compare the risk to two organs at risk, can be done more reliably.

This study established that VMAT can provide good target coverage to the prostate while minimizing bladder and rectal doses. The predictive model demonstrated here could be a good tool to use in conjunction with imaging and dose algorithms to optimize prostate treatment. Due to the high frequency of prostate cancer in men, a small decrease in secondary cancers could have a large effect on public health.

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