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Secondary cancer risk assessment after high-risk and intermediate-risk prostate cancer radiotherapy in Senegal

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Abstract

Purpose: This study aims at evaluating the excess absolute risk (EAR) of cancer in thirty patients with high and intermediate risks of prostate cancer based on the Amico's classification, who received a three-dimensional conformal radiotherapy (3DCRT) or a modulated volumetric arc therapy (VMAT) with 6 MV photons energy.

Materials and Methods: VMAT plans were performed in simultaneous integrated boost, with 76 Gy to prostate and 56 Gy to pelvic lymph node and seminal vesicle. 3DCRT planning was realized in two stages with prostate, seminal vesicles, and pelvic lymph node receiving 46 Gy, in the first stage, and in the second stage, prostate prescribed at 28 Gy. The EAR was assessed using the Schneider concept based on the equivalent dose for a given organ (OED). Thus, the EAR of the rectum, bladder, **pelvic** bone and healthy pelvic tissues were calculated and compared on the basis of the Mechanistic, Exponential Linear, Plateau and Sarcoma specific Mechanistic models.

Results: The EAR in the rectum were found to be higher in 3DCRT than in VMAT. The EAR values ranged from 3.98-5.37 for the rectum, and from 1.05-3.76 for the bladder depending on the model used.

Conclusion: The overall EARs analysis for both radiation modalities indicated that the risk of induction of carcinoma in the rectum was higher with 3DCRT, compared with VMAT. However, it would be necessary for validation of predicted models, to conduct prospective clinal trials with a larger patient cohort.

Keywords: Secondary cancer; Cancer risk; Prostate cancer; Three-dimensional conformal radiotherapy (3DCRT); Modulated volumetric arc therapy (VMAT)

1. Introduction

Prostate cancer is the second most common tumor in men [1]. In 2020, approximately 1.41 million of prostate cancer cases were identified worldwide [2]. Radiotherapy plays a key role in the management of prostate cancer. The development of radiotherapy technologies linked to the progress of information technology has made it possible to better target cancers while avoiding the surrounding organs at risk of secondary cancer. To this end, new treatment modalities have emerged, such as intensity modulated radiation therapy (IMRT), modulated arc therapy (VMAT), proton and heavy ion radiation therapy or hadrontherapy. In the case of prostate cancer irradiation, VMAT allows high doses to be delivered to the prostate, while reducing the dose to organs at risk and the treatment time [3]. A study by the European Association of Urology has shown that IMRT associated with hormone therapy is a treatment option for high-risk prostate cancer patients [4].

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The development of secondary cancers after radiotherapy is an adverse event that can be observed in the long term [5]. Indeed, patients cured of cancer may develop a second cancer after the initial treatment with radiotherapy [6]. The latency period may not exceed life expectancy, especially for pediatric patients [7]. Several factors including treatment technique, irradiated volume, type of tissue irradiated and radiological examinations are related to the radiation-induced secondary cancer [8].

During radiotherapy management, parts of the patient's volume within or outside the treatment field including organs at risk (OARs), may receive higher or lower doses. It is therefore important to assess the patient's risk of developing a secondary cancer that may have been caused by radiotherapy in Senegal, where such a study has never been done.

In this study, we assessed the risk of secondary cancer to organs at risk (OARs) after radiotherapy for high and intermediate risks prostate cancer using 3D conformal radiotherapy (3DCRT) and VMAT.

2. Material and methods

2.1. Treatment plans

Tomographic data from thirty patients, treated for high-risk or intermediate-risk prostate cancer according to the D'Amico classification, from 2019 to 2021, were selected for a retrospective planning study. Two different treatment plans were created for each patient with 6 MV photon of energy for each of the VMAT and 3DCRT techniques. Two planning target volumes (PTV1 and PTV2) were defined for each technique.

The VMAT technique was used for the patient's treatment plans. The PTV1 consisted of the prostate clinical target volume (CTV) with a margin of 3-mm posteriorly, and 7-mm in all other directions. PTV2 was the sum of the pelvic lymph node areas with a 5-mm margin, and the seminal vesicles with 3-mm posteriorly and 7-mm in all other directions. The mean volumes of PTV1 and PTV2 were 170±52cm^3 and 717±211cm^3 respectively. The planning was done using the simultaneous integrated boost technique with 2 arcs ranging from 160° to 200°. An isocenter was placed at the barycenter of the target volumes. The prescription at PTV1 and PTV2 was 38x2Gy and 38x1.47Gy respectively.

The 3DCRT was used to retrospectively plan all patients with 6 MV photon of energy. PTV1 consisted of the prostate, seminal vesicles and pelvic lymph node areas. PTV2 included only the prostate with the same margins as VMAT. The mean volume of PTV1 and PTV2 was 823±201cm3 and 170±52cm3 respectively.

The prescribed dose was 23x2Gy for PTV1 in the first stage, and a 14x2Gy boost to PTV2 in the second stage. Figure 1 shows the CTVs and OARs that have been defined.

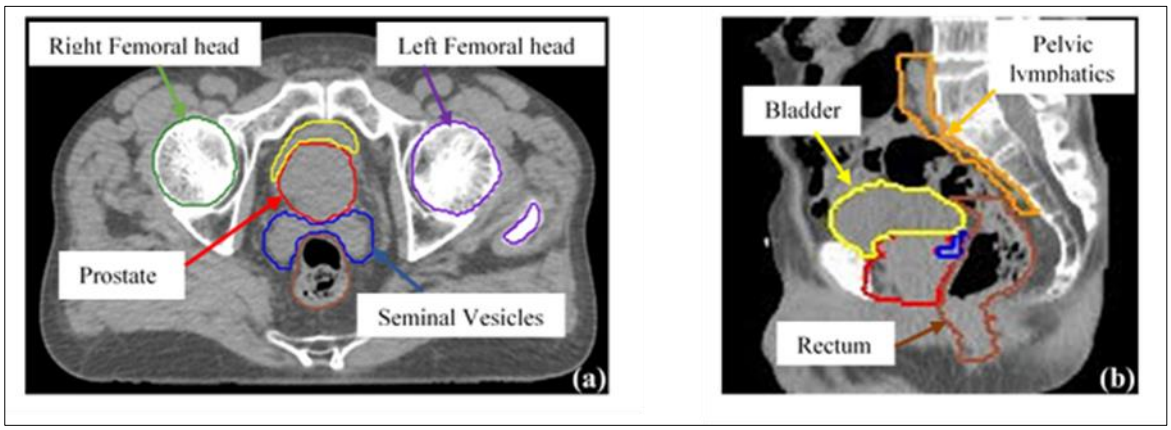

Figure 1 An example of the structure of the clinical target volumes (CTVs) and organs at risk (OARs) on the axial (a) and Sagittal (b) plans

For each of the realized plans, at least 95% of the PTV received 95% of the prescribed dose. The dose constraints to the OARs for each treatment modality presented were achieved (Table 1). In addition, bone and healthy tissue (the patient's CT volume in the grid minus the PTVs and OARs) were created. Dose-volume histograms (DVH) of the rectum, bladder, pelvic bones, and healthy tissues generated were extracted and used for the calculation of OEDs and EARs for each type of design.

Table 1 Dose constraints to the OARs according to the modalities VMAT [9] and 3DCRT [10]

OAR	Dose constraints VMAT	Dose constraints 3DCRT
Rectum	V70Gy ≤ 25%	V70Gy ≤ 20%
	V65Gy ≤ 35%	V65Gy ≤ 25%
	V60Gy≤ 50%	V50Gy ≤ 50%
Bladder	V70Gy ≤ 25%	V70Gy ≤ 35%
	V65Gy ≤ 50%	V65Gy ≤ 50%
Femoral Heads	V50Gy ≤ 10%	V50Gy ≤ 25%

2.2. Estimation of secondary cancer risk.

The absolute excess risk of developing solid cancer after radiotherapy is the absolute difference between the cancer rates of those exposed to a dose d and those not exposed to a dose above a natural exposition per 10 000 persons per year (PY) [11]. The mathematical expression for a small element of volume of the organ or tissue of the EAR is given by equation (1).

$$EAR(D, e, a) = EAR_0 . RED_D . \mu(agex, agea) \quad \text{.....(1)}$$

$$\text{Avec} \qquad \mu(agex, agea) = exp\left[\gamma_e . (agex - 30) + \gamma_a . ln\left(\frac{agea}{70}\right)\right] \quad \text{.....(2)}$$

EAR_0 is the slope of the dose-response curve at low dose, which values obtained from Schneider et al. [11] are presented in table 3. The risk equivalent dose **(**RED_D) translating the dose-response relationship for radiation-induced cancer into dose units. The function μ accounts for the age of the patient at the time of irradiation ($agex$), and the attainable age of the patient (($agea$). In our study, $agea$ was set to 85 years. γ_e and γ_a are age modification coefficients. EAR_0 was computed for patients exposed to radiation at the age of 30 years, the attainable age was 70 years.

When the dose-volume histogram of the organ of interest is known, its EAR is given by equation (3).

$$EAR_{org} = \frac{1}{V_t}\sum_i V_i . EAR_0 . RED(D_i) . \mu(agex, agea) \quad \text{..... (3)}$$

In equation 3, V_t is the total organ volume, the summation is extended over all intervals of the dose-volume histogram, and V_i is the volume of tissue *i* that received a dose D_i.

The dose-response relationship for high doses or for heterogeneous dose distributions is not linear [12, 13]. To better describe the non-linearity relationship, and estimate the effect of high doses, other dose-response functions are needed. For this purpose, the OED was introduced by Schneider et al. [13,14] assuming that two dose distribution in the organ are equivalent if they cause the same incident of radiation -induced cancer [13]. This concept, also known as Schneider's model, is a mechanistic model based on the linear-quadratic model and allows to predict cancer induction after fractionated radiotherapy [15]. The OED is a RED-weighted dose variable averaged over the entire organ volume. Its expression is given by equation 4.

$$OED = \frac{1}{V_t}\sum_i V_i . RED_{Di} . \quad \text{..... (4)}$$

Expression (1) becomes:

$$EAR_{org} = EAR_0 . OED . \mu(agex, agea) \quad \text{..... (5)}$$

With the Schneider model as described in Equation 5, the risk of observing radiation-induced secondary cancer is based on different models for calculating the OED (Equation 4) which accounts for assumptions regarding the behavior of cells after irradiation, and the dose-volume histogram of the organ [11,14].

2.2.1. Dose-response model of radiation-induced carcinoma

In the first step, the linear model that predicts a linear increase in radiation-induced cancer risk with dose is considered and translated into equation 6. In this model, the average dose to the organ can be used to assess the risk.

$$RED_{D_i} = D_i \text{..... (6)}$$

Then, the mechanistic model is considered which in addition to the cell death, mutation and repopulation/repair accounts for the fractionation of the treatment [11, 15]. The linear-exponential (equation 8) and plateau (equation 9) models were derived from the mechanistic model whose expression is given by equation 7

$$OED_{Mécanistique} = \frac{1}{V_t}\sum_i V_i \frac{e^{-\alpha' D_i}}{\alpha' R}.(1 - 2R + R^2 e^{\alpha' D_i} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D_i}) \text{.....(7)}$$

Where $\alpha' = \alpha + \beta.\frac{D_i}{n}$

The parameters α and β are obtained from the linear-quadratic model of cell death, describing the linear and quadratic response of the tissue to radiation. R describes the repopulation/repair of the irradiated cell in two dose fractions. It takes the value 1 if completed reparation of the cell is observed and the value 0 if no reparation occurs. Therefore, the values R=0 leads to the linear-exponential model as presented in equation 8. This model accounts for the fact that the cell death probability with the dose, implying a reduction of the risk of cancer induction due to the destruction of mutated cells. Moreover, the value R=1 reflecting complete cell repopulation/repair, represents the plateau model (Equation 9).

$$OED_{Linéaire-expo} = \frac{1}{V_t}\sum_i V_i e^{-\alpha' D_i} \text{..... (8)}$$

$$OED_{Plateau} = \frac{1}{V_t}\sum_i V_i \frac{1-e^{-\alpha' D_i}}{\alpha'} \text{.....(9)}$$

2.2.2. Dose-response model of radiated-induced sarcoma

Finally, we use the mechanistic dose-response relationship for sarcoma induction (Equation 10) which accounts for the death cell and the fractionation effect of the dose [15]. In this work, we consider an intermediate repopulation level R=0.5

$$OED_{Sarcome} = \frac{1}{V_t}\sum_i V_i \frac{e^{-\alpha' D_i}}{\alpha' R}.(1 - 2R + R^2 e^{\alpha' D_i} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D_i} - \alpha' R D_i) \text{.....(10)}$$

The absolute risk of radiation-induced carcinoma was computed for the rectum and bladder, and that of the radiation-induced sarcoma was computed for pelvic bones and healthy tissues according to Schneider model, accounting for the histogram of the 3DCRT and VMAT. The parameters used for the calculation of the EARs for each organ are presented in Table 2. They were calculated from data obtained from atomic bombing survivors and from Hodgkin's disease patients who received a single dose of radiotherapy between 2-40 Gy assuming a value of α/β equaled to 3 Gy for each organ [11].

Table 2 Parameters for EARs calculation

Organs	**EAR_0**	**Age factor**		**Carcinoma model**				**Sarcoma Model**	
				Mecha		**Lin-Expo**	**Plat**		
		γ_a	γ_e	**R**	α'**(Gy^{-1})**	α'**(Gy^{-1})**	α'**(Gy^{-1})**	**R**	α'**(Gy^{-1})**
Rectum	0.73	2.38	-0.024	0.56	0.033	0.031	0.065		
bladder	3.8	2.38	-0.024	0.06	0.219	0.213	0.633		
Pelvic bones	0.20	-0.56	-0.013					0.5	0.067
~~Heathy~~ **Healthy** tissue	0.60	-0.56	-0.013					0.5	0.060

Abbreviations: Mecha, Mechanistic; Lin-expo, Linear-exponential; Plat, Plateau.

2.3. Statistical analysis

The statistical analysis of the data was performed using SLSTAT version 2022.3.1 (Addinsoft (2022). XLSTAT statistical and data analysis solution. Paris, France. https://www.xlstat.com/fr). The descriptive analysis was done by computing the median, the mean, and the standard deviation. The student's T-test for paired sampled and the non-parametric Wilcoxon signed ranks test were performed. The P value < 0.05 was considered statistically significant at 95% confidence interval.

3. Results and discussion

We collected 30 patients, eighteen (18) of whom were at high risk and twelve (12) at intermediate risk. The mean age was 67.7 ± 6.25. Figure (2A) with concave isodose curves show an example of the dose distribution in the axial and sagittal planes obtained for the VMAT modalities, and Figure (2B) with rectangular isodose curves show the dose distribution in the axial and sagittal planes obtained for the 3DCRT modalities. Target volume coverage constraints, and dose targets at OARs were met for each modality.

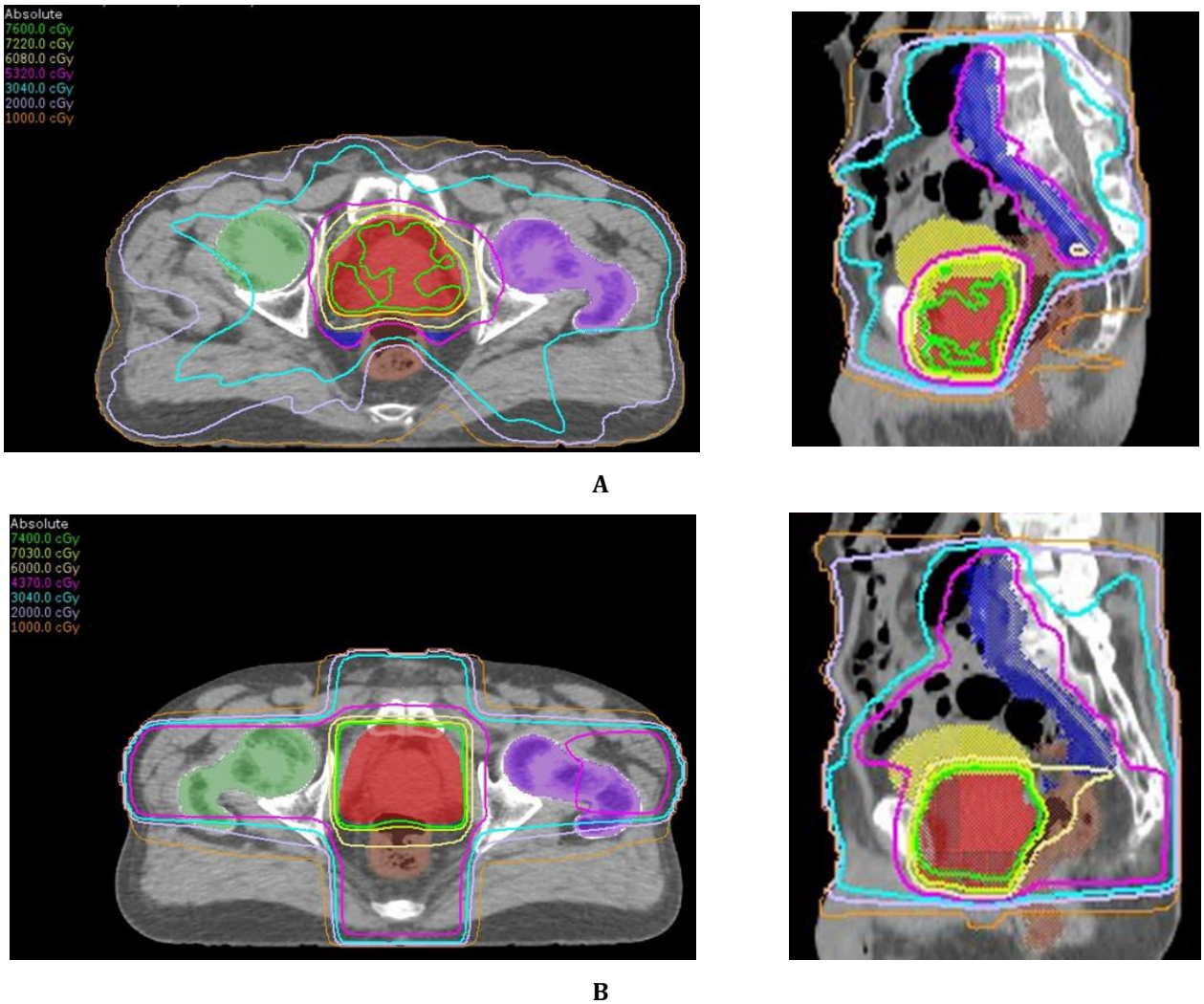

Figure 1 Examples of axials and sagittal plans showing the dose distributions (represented by the thick lines) obtained for a patient planned with VMAT (A) and 3DCRT (B) modalities. The PTV prostate is shown in red, lymph glands and seminal vesicles are shown in blue. The bladder, rectum, left and right femoral heads are respectively shown in yellow, brown, purple and green.

The mean values of rectal, pelvic bone and healthy tissue EARs calculated with several dose-response models are described in Table 3. For each model, the result is shown in Table 4. For each model, the presented result is the mean value over all patients for each treatment modality. The mean EAR for induction of rectum carcinoma and bladder is 4.33 and 2.18 per 10 000 PY respectively for VMAT, and 5.01 and 2.10 per 10 000 PY respectively for 3DCRT.

Table 3 Mean values and standard deviation of EAR computed over all patients for 3DCRT and VMAT techniques.

Plans		$EAR_{Carcinome}$					$EAR_{Sarcome}$	
	Rectum			Bladder			Pelvic bone	Healthy tissues
	EAR_{Mecha}	$EAR_{Lin-expo}$	EAR_{Plat}	EAR_{Mecha}	$EAR_{Lin-expo}$	EAR_{Plat}		
VMAT	4.55±0.78	3.98±0.69	4.47±0.77	1.61±0.28	1.20±0.23	3.74±0.62	0.21±0.03	0.33±0.05
p-value	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*0.07*	*0.11*
3DCRT	5.37±0.91	4.44±0.74	5.23±0.89	1.49±0.25	1.05±0.19	3.76±0.62	0.21±0.02	0.42±0.06
p-value	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*<0.05*	*0.94*	*0.12*

Abbreviations: Mecha, Mechanistic; Lin-expo, Linear-exponential; Plat, Plateau; for carcinoma dose-response model, and Sarcoma specific mechanistic sarcoma dose-response model. EAR unit is per 10 000 persons per year.

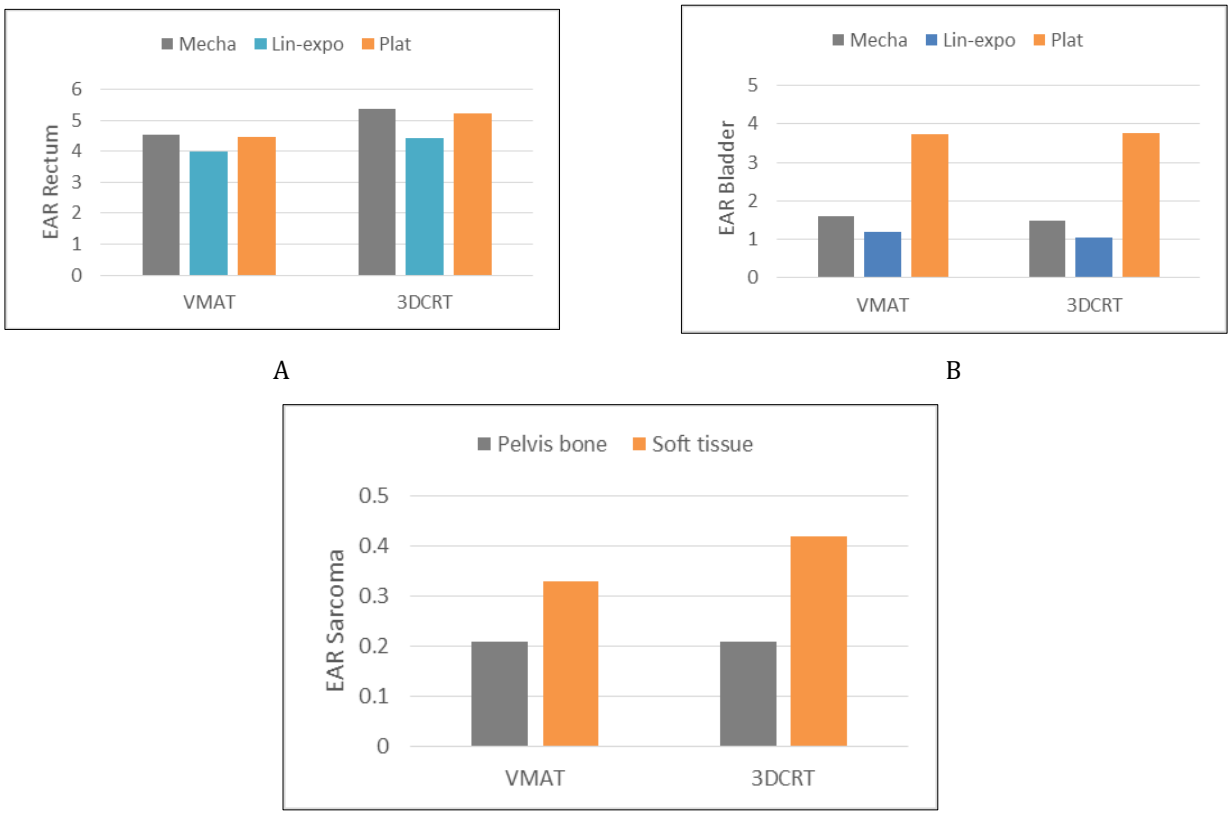

Figure 2 The excess absolute risk (EAR) of the rectum (A), bladder (B), Pelvis bone end soft tissue (C) for prostate irradiation. Calculation of the EAR based on differential dose-volume histogram-was performed using the full mechanistic (gray), linear-exponential (blue), and plateau (orange) dose-response model for the rectum and bladder. The EAR calculation was performed using the sarcoma model for the pelvis bone (gray) and soft tissues (orange). 3D conformal radiotherapy (3DCRT), volumetric modulated arc therapy (VMAT) was using with 6MV photon. The mean values per 10 000 PY per Gy averaged over all thirty patients are shown. Abbreviations: Mecha, Mechanistic; Lin-expo, Linear-exponential; Plat, Plateau

The results in table 3 show that the absolute excess risk of secondary cancer is higher for rectum than for the bladder. Figure 3 presents the EARs mean histograms obtained in table 3. Figure 3a shows that VMAT reduces the EAR for the rectum according to the mechanistic, linear-exponential and plateau models compared to 3DCRT. In contrast, for the bladder the secondary cancer risk varies slightly irrespectively of the technique (Figure 3B). Regardless of the plan, the relative difference of the predicted EAR according to the different carcinoma induction models is smaller for the rectum than for the bladder (p<0.05).

The absolute risk of sarcoma is low for pelvic bones and healthy tissue regardless of the plan. Despite those low sarcoma induction values, we observe that sarcoma induction at healthy tissue is higher than at pelvic bones regardless of the modality (p<0.05) (Figure 3 C).

Radiation-induced secondary cancer is one of the principal stochastic effects of radiotherapy. Estimation of risk of radiation-induced secondary cancer is becoming an important aspect for comparative treatment planning in radiotherapy. The actual planning system provide three-dimensional dose distributions for each patient, thus leading to new possibilities for more accurate estimates of the incidence of secondary cancer in irradiated organs. In this present study, we-showed the risks of radiation-induced secondary cancer in organs involved in prostate cancer treatment. We evaluated the absolute risk for plans performed in VMAT with simultaneous integrated boost and then retrospectively planned 3DCRT plans.

The patients included in this study were adults diagnosed with high risk and intermediate risk of prostate cancer. The patients' ages ranged from 52-81 at the time of exposure. The age at exposure is one of the main factors involved in radiation-induced cancer. Lower risks of secondary cancer induction have been reported for older cancer patients, mainly due to their short life expectancy relative to the required time for the carcinogenesis process to occur [16]. In addition, according to epidemiological studies, the radiation-induced secondary cancer risk does not generally decrease with increasing age at exposure [17, 18], but rather increases for adults over 40 years at the time of exposure [18]. Consequently, patients relatively old can be considered as an appropriate group for estimating the risk of radiation-induced secondary cancer. Several studies have been conducted on the potential increase in secondary cancer risk of IMRT techniques compared to conformal 3DCRT [19-21]. According to Rehman et al., the risk of secondary cancer induction for spine in VMAT is lower than in IMRT and 3DCRT [22]. Zwahlen et al. observed a small difference in the risk of secondary cancer in the bladder and the colon through VMAT and RT-3D modalities in rectal cancer irradiation [23]. A study by Fontenot et al. showed that the rectum and bladder have highest predicted risk of secondary cancer in pelvic radiotherapy [24].

Comparing the results obtained from the dose-response model for the bladder, we observe a significant reduction in the risk of secondary cancer according to the mechanistic and linear-exponential models compared to the plateau, irrespective of the modality. This could be explained by the reparation and repopulation effects of the mechanistic and linear-exponential models [11]. Regarding the rectum, the EARs for 3DCRT was higher than that of the VMAT. The fact that VMAT may reduce the risk of secondary cancer compared to 3DCRT was demonstrated by Rehman et al. [22], though its low dose distribution over a larger volume of healthy tissue is greater [25, 26]. This study also indicated that the risk of secondary sarcoma of the pelvic bones and soft tissues was low regardless of the plan and techniques, as highlighted by Haciislamoglu et al. [27] in his study.

The results obtained from our study according to the mechanistic model ranged from 4.55-5.37 and from 1.49-1.61 per 10 000 PY for the rectum and bladder respectively. Our results are lower than those obtained by Haciislamoglu et al. in his study on evaluation of EARs in cohort of 5 high risk prostate cancer patients, whose obtained values via the mechanistic model ranged from 7.13-7.94 and 2.16-2.44 per 10 000 PY for the rectum and bladder respectively [27]. This could be explained by the fact that the irradiated PTV volumes in their study is greater compared to ours. Murray et al. also conducted a study of three patients in which the rectum and bladder EARs is comprised between 1.44-2.69 and 1.70-2.42 per 10 000 PY respectively, using the mechanistic model for prostate cancer patients with the 3DCRT, IMRT, VMAT radiotherapy modalities with FF and FFF beams [28]. A direct comparison of their results with that of this study is less easy because the irradiated volumes were not specified in their study. However, it is quite possible that the volume of their PTVs is lower than our volume because the irradiated patients in their study had early-stage prostate cancer, therefore a non-pelvic irradiation. It is worth noting that for non-pelvic irradiation, the delivered dose to OARs is lower, contributing to-the reduction of the calculated EARs value.

The advantage of our study is that unlike the studies mentioned in our discussion, we evaluated the risk of secondary cancer with a larger cohort of patients. Other studies on similar cancer risk assessments also used a small number of patient cases, generally 2-3 per study. The main interest in this type of study is to show the difference between treatment modalities rather than the factors to interpatient variability, hence the relatively small sample size [24, 26, 29, 30]. In

the framework of this study, the impact of the dose due to the image-guided radiotherapy was not considered as it was not available for the–previously treated patients. Ardenfors et al. showed that the existence of an additional risk of radiation-induced cancer due to repeated repositioning imaging is very small [31]. These secondary cancer risk models also have uncertainties related to the concept of OED [11], as well as the assumptions that have been made to simplify the biological approximations leading to cancer induction [15].

4. Conclusion

In conclusion, this study demonstrated the risk of induction of secondary cancer in organs at risk after radiotherapy for high risk and intermediate risk prostate cancer, according to different dose-response models. The overall analysis of EARs for the two modalities of radiotherapy indicated that the risk of induction of carcinoma of the rectum was higher with 3DCRT than with VMAT. The risk of secondary cancer was lower at bladder than at the rectum irrespective to the treatment modality. The risk of sarcoma secondary to healthy tissue**s** and pelvic bone was lower for the examined plans. However, it would be necessary for validation of predicted models, to conduct prospective clin**ic**al trials with a larger patient cohort.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animal/human subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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