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Evaluation of NTCP and Second Cancer Induction from Modulated Arc Therapy for High-Risk Prostate Carcinoma by COUPÔLE Software

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ABSTRACT

Introduction: Assessing the toxicity and the risk of radiation-induced secondary cancer is crucial for optimizing treatment planning in prostate carcinoma patients with high risk undergoing Volumetric Modulated Arc Therapy (VMAT). This study aims to evaluate normal tissue complication probability (NTCP) and excess absolute risk (EAR) for different structures (organs at risk, the body). The developed in-house software COUPÔLE was used for toxicity and risk estimation and verified against BIOSUITE.

Material and Methods: A cohort of twelve randomly selected patients treated with 76 Gy (2 Gy/fraction) using a 6 MV (ELEKTA) treatments were analyzed. Treatments plans were generated using the MONACO system.NTCPs were calculated for rectal bleeding, fecal incontinence and bladder contracture endpoint, while secondary cancer risks were estimated using differents radiobiological models(the Linear Quadratic (LQ), Schneider Linear Exponential and Plateau model) for rectum, bladder, and whole body.

Results: NTCP values of 6.6% and 5.7% for rectal bleeding and bladder toxicity (COUPÔLE vs. BIOSUITE) and 5.3% and 5.4% for fecal incontinence. No bladder toxicity was observed. The estimated risk for rectum and bladder (LQ model) were 0.06 (0.02-0.15) and 0.01 (0.0-0.03), respectively. Using the Schneider model, whole-body risk reached 5.40% for V50Gy. The risk was notably higher for the rectum than for the bladder, highlighting the need for further optimization.

Conclusion: These findings confirm the reliability of COUPÔLE for NTCP and secondary cancer risk estimation, demonstrating its applicability for clinical decision-making in radiation oncology.

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Introduction

Prostate cancer is the third most common cancer in men worldwide, after colorectal cancer and lung cancer. Approximately half a million cases occur each year [1,2]. By 2020, the number of cases is expected to reach 10 million, with 7 million deaths, particularly in developing countries. In Algeria, prostate cancer is the fourth most common cancer in both sexes, with an incidence rate of 6.2%, and second in men, with an incidence rate of 13.2%. In Algeria, 3,597 new cases were recorded, with 1,635 deaths in 2020[3].

The principal treatments for cancer include surgery, chemotherapy, radiation-therapy, immunotherapy and hormonal therapies. In this study, patients were treated with external radiation-therapy.

Intensity-Modulated Radiotherapy (IMRT) is a widely used radiation-therapy treatment modality for prostate cancer [4,5]. IMRT was first introduced in clinical practice around 1995. In addition to providing homogeneous and highly conformal tumor dose distributions, IMRT offers several other benefits [6].

IMRT enables superior sparing of normal tissues across various tumor sites. Considerable progress has been made in cancer treatment over the last decade, leading to a more precise definition of the treatment target and the organs at risk (OARs), as well as improved dose distributions that ensure good tumor control and reduce the dose to organs at risk. However, there remains a finite probability of inducing second cancer. For physicists who work with radiotherapy, minimizing the toxicities associated with radiotherapy remains a priority [7].

While, with the introduction of Volumetric Modulated Arc Therapy (VMAT), we can provide rotational intensity modulated therapy with more degrees of freedom. A meta-analysis that compared VMAT with IMRT revealed that the VMAT technique, delivered with 6 MV photons generated by a Linear accelerator, can be considered the preferred approach

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for the treatment of prostate cancer due to its superior delivery efficacy [8].This technological development aims to achieve the main objective of treatment planning, which is to find the right option to satisfy two conflicting priorities, such as the concentration of the prescribed dose in a target volume and the reduction of the dose received in the organ at risk.

Radiation-induced cancer is one of the major late risks following radiotherapy. It is therefore inevitable that models to assess the risk of developing a second cancer will have to be developed and used in epidemiological studies and to assess the risk of developing a second cancer [9,10].

To make predictions for new treatments for which there is no clinical evidence, induced cancers are derived from data on Atomic Bomb Survivors. The shape of the dose-response curve for radiation-induced cancer for doses above 1 Gy in patients receiving radiotherapy is not always easy to establish because it is difficult to know how the risk of radiation-induced cancer varies with dose (whether it remains Linear or decreases or stabilizes at high doses due to cell destruction)[11].With this in mind, this study was designed to estimate the risk of secondary cancers in organs at risk, namely the bladder, rectum and all healthy tissues in the body, in case of prostate cancer treated with the VMAT technique.

For this purpose, a number of mathematical models for the normal tissue complication probability (NTCP) have been developed by physicists, including the one created by Lyman-Kutcher-Burman (LKB) [12, 13]. Another area of concern for physicists is the prediction of the risk of radiation-induced cancer following radiotherapy. In this study, we have chosen to estimate the risk of induced second cancer using the Linear model recommended by the United Nations Scientific Committee on the Effect of Atomic Radiation (UNSCEAR) [14] and various predictive models based on the concept of the organ equivalent dose as developed by Uwe Schneider [15].

To this end, in-house software was developed, namely "COUPÔLE". It incorporates radiobiological metrics such as Equivalent Uniform Dose (Niemierko, 2007) [16] and normal tissue complication probability using the LKB model. The results were benchmarked against those obtained by BIOSUITE [17]. Additionally, we estimated the probability of developing a second cancer following radiotherapy using the UNSCEAR method, the Linear Exponential and Plateau Model, for all structures (rectum, bladder) and the body.

Materials and Methods

A total of twelve cases of patients treated for high-risk prostate carcinoma were studied during 2021 at the radiation-therapy department of Fatema El Azhar Centre of Algiers. The median age of these patients was 75 years, with stratifications ranging from T2aN0M0 to T3bN0M0 and no indication of metastatic spread. These patients exhibited a specific antigen (PSA) level greater than 20 ng/ml and a dominant Gleason score of 8 to 10.

The prescribed dose was 76 Gy, delivered in a daily fraction of 2 Gy to the Planning Target Volume (PTV), from Monday to Friday inclusive. All patients were treated with RapidArc (RA), using single arcs in two directions clock wise(CW) and counter clock wise (CCW), with one single arc spanning 360 degrees. The angulation varied from 192° to 166° with 30° increments, and the arc opening of 30° was set to avoid posterior rectal irradiation, as recommended in reference [18].

All plans were delivered with a 6MV beam (VERSA HD Linear accelerator) and modulated with a 160-leaf collimator with a leaf thickness of 0.5 cm. In accordance with the Radiation Therapy Oncology Group (RTOG) 1106 report[19](Table 1), the tumor and organs at risk were defined and contoured by a radiation oncologist on the MONACO software (version 5.11.02, ELEKTA).

Table1. Definition of different Target's volumes

	Prostate carcinoma with high risk
CTV1	GTV + ganglions with margin of 5 mm
PTV1	CTV 1 + margin of 8 mm and 5 mm in posterior
CTV2	GTV
PTV2	CTV2 + margin of 8 mm and 5mm in posterior
GTV	Prostate

All treatment plans were developed, generated and optimized using the same objectives in accordance with the Michel Bolla et al. constraints defined for the rectum and the bladder [20] (Table 2). The Treatment Planning System (TPS) Monaco utilizes a variety of tools, including the homogeneity index, conformity index and gamma index, to ensure high-quality treatment plans with optimal dose distributions [21].

Table2. Constraints dose defined for Rectum and Bladder in the case of high-risk prostate cancer
treated with VMAT. [20]

Structures	Constraints	Maximum Dose
Rectum	V30< 60%	D_{max}< 76 Gy
	V60<50%	
	V70< 25%	
Bladder	V74< 5%	
	V60<50 %	D_{max}< 82 Gy
	V70< 25%	

Dosimetric metrics assessment

To assess the efficacy of the treatment, a number of dosimetric metrics were employed, including the dose volume histogram, statistical doses such as D_{min}, D_{max}, and D_{mean}, as well as constraints, to evaluate and analyze both the target and surrounding normal structures (OARs).In practice, we aimed to maintain a degree of heterogeneity within the prescribed dose range of +7% to -5%, in accordance with the International Commission on Radiation Units (ICRU) report

62[22].We calculated the dose conformity index (CI) and target homogeneity index (HI) using the following equations given in ICRU report 83[23]; In practice we try to have CI =1 and HI<10%.

$$CI = \frac{V95\%}{V(PTV)} \quad (1)$$

$$\mathrm{HI} = \frac{\mathrm{D2\%-D98\%}}{\mathrm{D50\%}}. \quad (2)$$

Where:

$V_{95\%}$: the volume receiving at least 95% of the prescribed dose;

PTV: the planning target volume;

V(PTV): volume of the planning target volume

$D_{2\%}$:is the maximum dose in 2% volume of the PTV;

$D_{98\%}$: is the minimum dose in 98% volume of the PTV;

$D_{50\%}$: is the median dose

Modeling "NTCP" and analysis of Toxicity for organs at risk

In this part, our study was focused on investigating the NTCPs (Kutcher and Burman, 1989)

[24,25] for rectum and bladder toxicity variation.

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \exp\left(-\frac{t^2}{2}\right) dt \quad (3)$$

$$x = \frac{D - TD_{50}}{mTD_{50}} \quad (4)$$

$$TD_{50}(v) = TD_{50}(1) \times v^{-n} \quad (5)$$

$$\mathrm{v} = \frac{V}{V_{ref}} \quad (6)$$

where;

v: is the relative volume irradiated to a dose D;

V: is the total volume of organ of interest;

V_{ref}: is the ref volume of organ receiving the prescribed dose;

In COUPOLE software, Kutcher and Burman model was used and the volume of an organ was reduced into an effective volume v_{eff} [26]. In this volume, the irradiation is uniform and gave the same toxicity as the non-uniform irradiation. v_{eff} is given by the following equation:

$$\mathrm{V_{eff}} = \sum_{i=1}^{n} v_i \times \left(\frac{D_i}{D_{ref}}\right) \quad (7)$$

Where:

n, m are obtained from estimation of the tolerance doses for uniform whole and partial organ irradiation;

$TD_{50}(1)$: is the tolerance dose for 50% complications for uniform whole organ irradiation

$TD_{50}(v)$: is the 50% tolerance dose for uniform partial irradiation to the partial volume V.

vi: partial volume of organ;

Di: dose which corresponds to irradiated partial volume of interest (organ).

NTCPs were computed using in-house software (COUPÔLE)writing with FORTRAN language and compared with BIOSUITE for rectum and bladder. The toxicities were calculated for grade 2-3 rectal bleeding(TD_{50}=97.7, m=0.27, n=0.085, α/β=3)[27,28], as well as for grade 3 faecal incontinence (TD_{50}=105 Gy, m=0.43, n=1, α/β=3; (Rancati,2008) [29] and bladder contracture (grade ≥2, TD_{50}=80Gy, m=0.11, n=0.5, α/β=3) (Burman,1991)[30].

In order to conduct a statistical analysis, a 95% confidence interval was set and a significant level was set at α = 0.05; so the paired t-test was performed to compare the results;

Second cancer risk of carcinoma and sarcoma estimation

First model: Most cancer incidence data are based on second cancers close to the target. Dorr and Hermann [31] found that between 60% and 90% of second cancers occur at 5 cm from the edges of the treatment field. Bioce et al. found that 43% of second cancers developed close to the primary field, Hall et al [32] showed that the risk of cancer increases in Linear proportion to dose at low and moderate doses (between 0.1 and 3 Gy).

In this study, we have tried to quantify the risk of developing a second cancer in the rectum and bladder and in the body (healthy tissue +PTV). The method used is based on the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). In this model, we consider two terms and different factors that take account of DNA mutation and cellular survival for a fractionated treatment plan [33].

The mathematical model is given as:

$$\mathrm{Effect} = \left(\alpha_1 D + \beta_1 \frac{D^2}{n}\right) exp\left[-\alpha_2 D + \beta_2 \frac{D^2}{n}\right] \quad (8)$$

Where:

n: number of fractions;

D: is the mean dose given to the patient in n fractions;

α_1, α_2: are Linear factors of induction of DNA mutation and the cellular survival;

β_1, β_2, are quadratic factors.

The values of these parameters are provided from the literature and are based on clinical and experimental data (Table 3).

For each OARs, it is assumed that $\alpha_1/\beta_1 = \alpha_2/\beta_2$;

Table3. α_1 and α_2 are the Linear factors of DNA Mutation and cellular survival processes. [33]

Parameters	Bladder	Rectum
α_1 (Gy^{-1})	0.006	0.017
α_2 (Gy-1)	0.25	0.25
α_i/β_i (Gy)	7.5	4.5

Second model: In this part of the study, the Schneider model was used for rectum and bladder. Firstly, the dose response was defined after administration of all the "n" fractions, where the rate of secondary cancer incidence

is proportional to the number of mutated cells relative to the number of stem cells before treatment [34]. The dose response was defined by the following equation as:

$$I^{org} = I_0^{org} \times Dexp(-\alpha_{org} D) \quad (9)$$

Where:

I_0^{org}: is the radiation induced cancer incidence rate at low dose for organ which estimate the absolute excess risk per 10,000 patient's/y/Gy;

α_{org}: is an organ-specific cell sterilization parameter.

I^{org}: is the absolute excess risk per 10,000 patients annually [35].

After the definition of the dose response, the Organ equivalent Dose (OED) for radiation –induced cancer, can be calculated using the Linear Exponential Model defined as [36]:

$$\mathrm{OED}_{\mathrm{org}} = \frac{1}{VT}\sum_{i=1}^{N} Vi \times Di \times \exp(-\alpha_{org} \times D_i) \quad (10)$$

Where the sum is taken over N dose calculation points related to the volume of the organ. The values of the different parameters are summarized in Table 4:

Table4. I_0^{org}Absolute excess risk per 10,000 patient's/y/Gy), α_{org} is an organ -specific cell sterilization parameter(R=0).

Parameters	Bladder	Rectum	Body*
α_{org} (Gy^{-1})	1.592	0.031(R=0)	0.08
I_0^{org} (Gy-1)	1.62	-	29.7

*The α value used is related to solid tumors in the body, [37,38].

Third model: The last model used is Plateau, defined by the following equation considering full repopulation "R=1",[39]:

$$\mathrm{OED} = \frac{1}{\mathrm{V}}\sum_{\mathrm{i}}^{\mathrm{N}} \mathrm{V_i} \times \left(\frac{1\text{-}\exp(-\alpha' \mathrm{D_i})}{\alpha'}\right) \quad (11)$$

Where:

$$\alpha' = \left(\alpha + \beta \frac{D}{D_T} d_T\right) \quad (12)$$

α' : is the cellular destruction parameter;

V: is the total volume of organ;

V_i: is the partial volume of organ;

D_i: is the dose received at the partial volume Vi

d_T: is the fraction dose;

α(rectum) =0.065 Gy^{-1} , R=1: full tissue recovery between dose fractions.

In case of the body, the Excess Absolute Risk "EAR" was calculated according to the equation bellow: [39,40]

$$\mathrm{EAR} = \mathrm{EAR_0} \times \mathrm{OED} \quad (13)$$

EAR_0: is the Excess Absolute Risk for Radiation induced cancer at a low dose from the Atomic Bomb Survivors (EAR_0=112,1) [35,41]

Results

Dosimetricevaluation

In Figure 1, dose distributions are plotted in coronal, sagittal and axial directions and dose- volume histograms (DVHs) were used to provide dosimetric evaluation of tumor, organs at risk and the body in terms of D_{min}, D_{mean} and D_{max}.Table 5 illustrates that all VMAT plans were satisfied with a minimum of 95% prescribed dose to the PTV. CI and HI were calculated and their values confirm a good Conformity between the tumor and the PTV CI ≤ 1 and good homogeneity of dose HI ≤ 10%. InTable5, we summarize all calculated doses (D_{min}, D_{mean}, D_{max})to OARs with a D_{max} lower than the constraints defined by RTOG D_{max}(rectum)<76 Gy and D_{max}(bladder)<82 Gy. Lower doses were noticed to the body (healthy tissues) due to scatter and leakage radiation from gantry head.

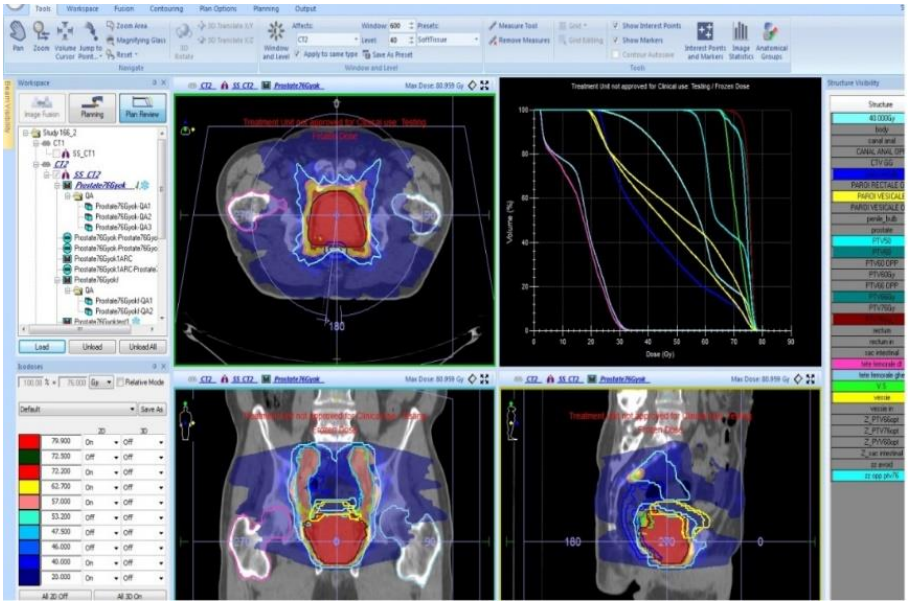


Figure 1.Coronal, sagittal and axial views of the VMAT planned dose distributions and dose-volume histograms have been plotted for tumor and Organs at Risk.

Biological evaluation

Normal Tissue Complication Probability modeling

To verify our in-house software (COUPÔLE), we estimated toxicities for organs at risk by calculating NTCPs for the rectum and bladder using dose-volume histogram data. NTCPs were calculated for these organs at risk, taking into accounts complication probabilities for uniform whole organ and partial organ irradiation.

Table 6 summarizes and compares all NTCPs values calculated using BIOSUITE and COUPÔLE for the rectal bleeding (NTCP1), fecal incontinence (NTCP2) and bladder contracture (NTCP3) endpoints.

A good similarity between the two software (COUPÔLE and BIOSUITE) particularly in the case fecal incontinence (NTCP2), and bladder contracture (NTCP3) endpoint. Some results are underestimated (patient: 2 and 7) and overestimated (Patient:4) and the discrepancy vary from (-1.6-6%) and (0%) respectively. Otherwise, all the results are in good agreement with BIOSUITE.

Table5.Statistical doses (D_{min}, D_{max}, D_{mean}, and V_{mean}) obtained over the different planning target volumes (PTV76, PTV66, PTV54) for Prostate and Organs at Risk (Rectum, Bladder, Rt- and- Lt-Femoral Head).

Tumor/PTVs	Dmin(Gy)	Dmax(Gy)	Dmean(Gy)	Vmean(cm^3)
Prostate	69.98±2.34	80.57±0.57	73.11±9.53	55.57±25.05
HI	1.05±0.013			
PTV76	63.95±3.97	80.85±0.71	75.59±0.01	125.88±43.38
CI	0.96±0.01			
HI	1.07±0.01			
PTV66	56.69±7.83	80.83±0.73	71.84±5.74	139.04±72.23
CI	0.99±0.01			
HI	1.16±0.032			
PTV54	41.54±3.32	80.08±2.79	59.63±2.92	940.50±185.54
CI	0.97±0.02			
HI	1.42±0.08			
Organ at risk and Body				
Rectum	9.91±4.92	67.82±20.97	33.58±9.33	52.69±22.66
Bladder	18.96±5.07	79.49±1.61	43.63±3.89	105.70±57.11
Rt-Femoral Head	2.33±2.93	48.64±8.22	19.86±4.39	167.00±31.41
Lt-Femoral Head	2.54±3.63	46.64±6.50	18.64±2.66	168.79±32.44
Body	0.095±0.044	77.35±3.19	12.19±1.25	20983.39±5310.61

D_{min}:Minimumdose;D_{max}:Maximumdose;D_{mean}:Meandose;V_{mean}:Mean volume;
*CI:*Conformity index*; HI:*Homogeneity index; *Rt:* right; *Lt:* Left

Table 6. Rectal and Bladder toxicity results using COUPOLE compared to BIOSUITE

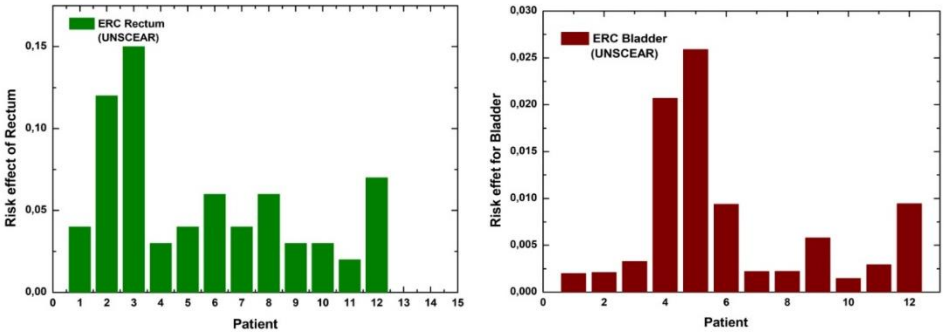
Rectum Endpoints					Bladder Endpoint	
Patient	NTCP1-Bleeding (%)		NTCP2-Incontinence (%)		NTCP3-Contracture	
	BIOSUITE	COUPÔLE	BIOSUITE	COUPÔLE	BIOSUITE	COUPÔLE
1	5.7	5.72	6.5	6.1	0.2	0.2
2	4.2	4.4	4.0	4.1	0.0	0.0
3	5.2	5.1	3.7	3.7	0.0	0.0
4	7.8	7.0	5.9	5.7	0.0	0.1
5	3.8	5.6	5.2	5.1	0.0	0.0
6	6.8	7.2	4.7	4.6	0.0	0.0
7	7.9	9.5	6.0	6.1	0.0	0.0
8	4.2	4.95	4.8	4.7	0.0	0.0
9	5.0	7.6	6.1	6.1	0.0	0.0
10	7.7	8.3	6.6	6.6	0.0	0.1
11	6.1	9.7	7.3	7.2	0.0	0.0
12	4.2	4.69	4.4	4.3	0.0	0.0

Table 7. Normal Tissue Complication probability "$NTCPs_{mean}$"and corresponding *p*-value of paired t-test for Rectal Bleeding, Fecal incontinence and Bladder Contracture endpoints.

Structures	NTCPs	COUPÔLE	BIOSUITE
Rectal Bleeding	Mean (%)	6.6[4.4-9.7]	5.7 [3.8-7.9]
	t-test:	p<0.26	p<0.12
Fecal Incontinence	Mean (%)	5.3 [3.7-7.3]	5.4 [3.7-7.3]
	t-test:	p<0.71	p<0.82
Bladder Contracture	Mean (%)	0.03[0.0-0.2]	0.02[0.0-0.2]
	t-test:	p<0.06	p<0.05

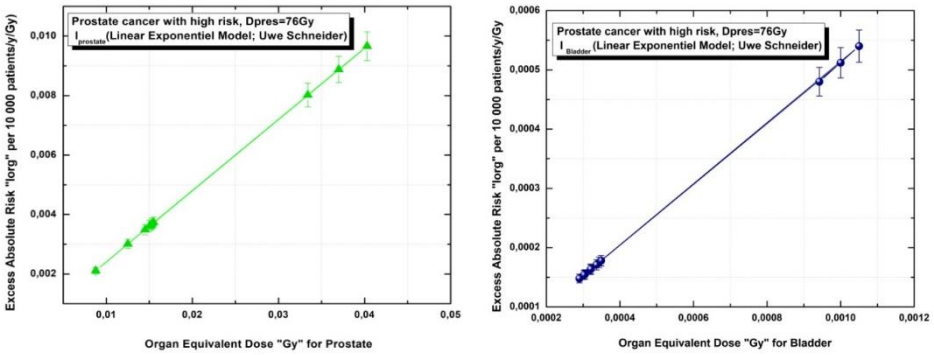
Second cancer risk estimation

The risk of developing a second cancer using the Linear Effect Risk equation (UNSCEAR) was estimated for rectum and bladder using (LQ) model was 0.06(0.02-0.15), p<0.008 ;0.07 (0.001-0.03) (p<0.001) for rectum (Figure2A) and bladder (Figure 2B) respectively.



(A) (B)

Figure 2. Risk for secondary cancers for Rectum (A) and for Bladder (B) (Effect of the risk model (UNSCEAR))



(A) (B)

Figure 3. Excess Absolute Risk for prostate (A) and Bladder(B) (Uwe Schneider model).

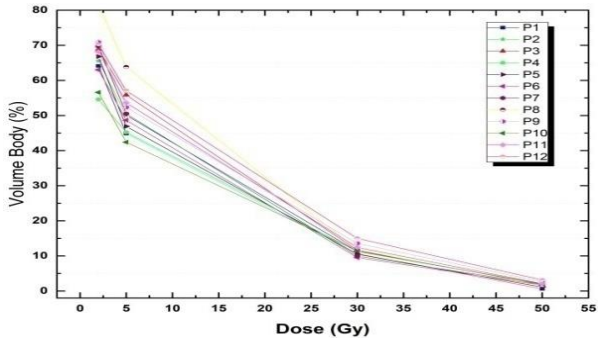


Figure 4. Irradiated volume (%) in the body to a dose of 2, 5, 30 and 50 Gy for each patient

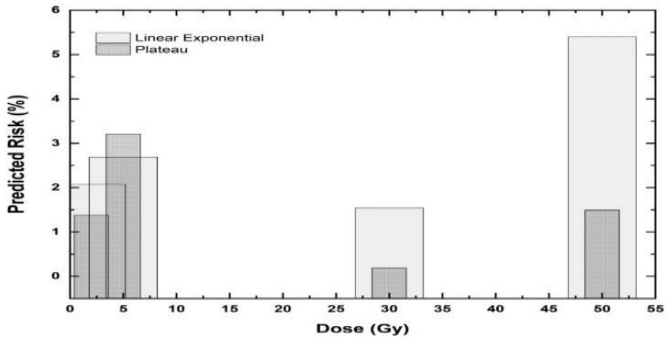


Figure 5. Predicted risk (%) as a function of the dose delivered at $V_{2\,Gy}$, $V_{5\,Gy}$, $V_{30\,Gy}$and $V_{50\,Gy}$in the body using Linear Exponential and Plateau models.

Table8. Percent volumes (%) and associated risk of induced second cancer in the body receiving a dose of 2Gy, 5Gy, 30 Gy and 50Gy in 38 fractions.

	Carcinoma in the body (D <6Gy)		Sarcoma in the body (D<60 Gy)	
$Volume_{intheBody}$ (%)	V_{2Gy} (%)	V_{5Gy} (%)	V_{30Gy} (%)	V_{50Gy} (%)
	66.68	50.93	11.56	1.87
Models	Risk of induced second cancer (%)			
Linear Exponential	2.08	2.69	2.25	5.40
Plateau	1.38	3.21	0.19	1.49

In the Schneider Linear Exponential model, the organ equivalent dose (OED) and corresponding excess absolute risk (I_{org}) for prostate were estimated to be (0.02±3.1) Gy (p<0.003) and 0.0047 per 10,000 patients/year/Gy, respectively, with (p<0.000) (Figure 3-A). For bladder, the OED values are too low and close to "0" so the corresponding risk are negligible when using the Linear Exponential Model (Figure 3-B).

In addition to rectal and bladder toxicity and risk, the probability of carcinoma or sarcoma induced in the body after radiotherapy was investigated. The fractional volumes received in the whole body at a dose of 2 Gy, 5 Gy, 30 Gy and 50 Gy were analyzed and the associated risk was modeled using Linear Exponential and Plateau models.

From the fractional volume receiving a dose of V_{2Gy}, V_{5Gy}, V_{30Gy} and V_{50Gy} plotted for each patient function dose delivered in 38 fractions, it was found that the higher doses were received in the smallest volume (Figure 4).Table 8 summarizes all the results obtained for carcinoma and sarcoma induction after radiotherapy for the entire cohort. For carcinoma induction (D<6Gy), the risk is more important (3.21%) in case of the Plateau model, but for sarcoma induction (D<60Gy), especially for V_{50Gy}, the risk was higher and reached 5.40% when using the Linear Exponential model. Figure 5 illustrates the estimated risk (%) with the two models, where the maximum obtained with V_{50Gy}, make the risk more critical for this fractional volume in the body in the case of Linear Exponential model.

Discussion

Dosimetric evaluation revealed that all the average doses to the target volumes (PTVs) were within the specified criteria and exhibited a high conformity index and high dose homogeneity. In this trial, improved rectal and bladder sparing was achieved with volume-modulated arc therapy and the dose objectives for rectum and bladder met the criteria of the QUANTEC reports (calculated Dmax(rectum)<76Gy and Dmax(bladder)<82Gy). The rotating arcs planned with VMAT provided effective conformal doses and deliver lower doses so assure better protection of organs at risk [42].

Regarding toxicity, Tables 5 and 6 illustrate all the values obtained for the different structures (rectum and bladder) and show that VMAT had the highest sparing of OARs with a lower NTCP. These results are in good agreement with those obtained by Clemente in the case of the bladder (NTCP<<0), in the case of the rectum the calculated NTCPs with BIOSUITE and COUPOLE are lower than those obtained by Clemente (NTCP=11.1%) [43].

In case of rectal bleeding, we noticed that 30% of the obtained results are overestimated this due to the data of patients. On the other hand, a good agreement between our results and those obtained by J. Uzan et al [27]where the calculated NTCP was 5.10% (7.2-7.6%) in case of prostate cancer treated with 85 Gy (boost on PTV). The difference between COUPOLE and this study is related to the adopted schedule.

Concerning the estimated observed risk using these three models: LQ effect risk (UNSCEAR), Linear Exponential and Plateau model (Uwe Schneider) for rectum and bladder and body indicates that the risk is more important for rectum (2-15%) ((Figure 2A), when using LQ model. It was found that the clinically observed risk is in the range of (0.05-0.20%), and (0.15-0.32%) for rectum and bladder respectively [44].

Regarding the induction of second cancers after radiotherapy, the two OARs selected and studied showed the highest average risk of a second cancer for the rectum. These values are lower than those obtained by Mazonakis et al, (1.59-5.82%) because he used Mechanistic model in this study [45].

In this part, the result obtained for calculated risk for carcinoma and sarcoma induction after radiotherapy in the body (Table 8) show that the Linear Exponential model present a higher increase of risk compared to the Plateau model, especially for V_{50Gy}, which reaches a value of 5.40%.Despite the smallest irradiated volume receiving a dose of 50Gy (Figure 4), It was previously found that the risk of sarcoma was 30 times higher after 44 Gy[46].The probability to develop a sarcoma in this region in the body is critical.

Conclusion

The aim of this study is to evaluate the VMAT modality dosimetrically against the constraints initially defined by the physicist and the RTOG.

Higher levels of toxicity were observed in the rectum than in the bladder when VMAT was used, and the risk of sarcoma increased when the dose was higher than 50 Gy. COUPOLE is still on improvement for some other models.

This study constitutes the primary data for the radiobiological evaluation of new radiotherapy modalities in Algeria. For better statistical results, more patients could be assessed for toxicity and risk after radiotherapy, especially when advanced treatment modalities are involved.

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