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Secondary cancer risk estimation following prostate cancer radiotherapy through gEUD concept and NCRP-116 recommendations

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ABSTRACT

Background: Radiotherapy is one of the practical modalities in prostate cancer treatment, but there is a risk of developing secondary cancers caused by unintended radiation inside the non-target organs. The current study aimed to evaluate the risk of secondary cancer development in organs at risk (the bladder and rectum) following prostate cancer radiotherapy. ***Materials and Methods:*** A group of 39 patients with prostate cancer who were treated with 3-dimensional conformal radiotherapy (3D-CRT) were enrolled. A dose-volume histogram (DVH) corresponding to each patient was utilized to estimate the absorbed dose for the rectum and bladder and to calculate their respective generalized equivalent uniform dose (gEUD). Finally, the risk of secondary malignancies was estimated by employing the gEUD values and recommended risk factors by the National Council on Radiation Protection and Measurements (NCRP) 116. ***Results:*** The gEUD values for the rectum and bladder ranged from 50–75 and 25-80, respectively. The mean gEUD values for the rectum and bladder were correspondingly equal to 60.97 Sv and 53.74 Sv, respectively. The mean secondary cancer risk (SCR) value for the rectum was 30.4%, while about 16.1% was estimated for the bladder. The estimated SCR in the rectum was 1.88 times higher than in the bladder. ***Conclusions:*** The rectum is more exposed to radiation and is endangered by the development of secondary cancer following prostate cancer radiotherapy. Nevertheless, the probability of cancer incidence in the bladder was also considerable.

INTRODUCTION

Prostate cancer has been known to be the most common and second-leading cause of cancer-related death among men worldwide [(1)]. During 27 years of monitoring in Iran, the incidence rate of prostate cancer in 1991 was estimated at 2.2 per 100,000 people, while it increased to about 24.8 per 100,000 people in 2018 [(2)]. Different modalities have been introduced for prostate cancer treatment. Radiotherapy is considered one of the most effective methods and is essential in controlling the risk of local tumor reoccurrence [(3)]. Subsequently, radiotherapy has made a prominent contribution to cancer treatment, so that approximately more than two-thirds of cancer patients are treated by the technique [(4)]. Although radiotherapy has a well-established advantage, it has been proven that it may increase the probability of developing secondary cancers [(5)]. After the radiotherapy techniques, the risk of developing secondary cancers caused by primary and scattered radiation within the non-target organs is considerable. Regarding more than ten years of follow-up, the probability of developing secondary cancers relevant to the radiotherapy techniques is about one in 70 patients [(6)]. About 70% of secondary cancer developments following prostate cancer radiotherapy occur in surrounding healthy tissues such as the bladder and rectum, the organs at risk (OARs) directly exposed to radiation [(7-10)].

Today, high-energy radiotherapy techniques deliver the highest dose to the target and the lowest dose to non-target healthy organs. Sanchez-Nieto *et al.* [(11)], determined the effect of low environmental

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doses and, subsequently, the risk of primary and secondary cancers during intensity-modulated radiotherapy (IMRT) and volumetric intensity-modulated arc therapy (VMAT) versus 3-dimensional conformal radiotherapy (3D-CRT). It was observed that IMRT and VMAT not only did not reduce the absorbed doses inside the organs at risk, but the doses of non-target organs associated with VMAT and IMRT were about three times higher than 3D-CRT. This means that applications of the IMRT and VMAT techniques may increase subsequent secondary cancer risks (SCRs). Owing to the importance of the patient's anatomy for assessing secondary cancers, Stokkevag et al. [12], investigated the influence of inter-fractional organ motions on SCR during the VMAT and intensity-modulated proton therapy (IMPT) radiotherapy methods. It has been found that there is a significant difference in the relative risk of secondary cancer in patients with prostate cancer when considering organ motions [12]. Furthermore, daily variations in the patient's anatomy affect the relative cancer risks inside the near-healthy organs [12]. Since the risk of secondary cancer induction, relevant to radiotherapy techniques, is unavoidable, estimating the relevant risk is critical. Furthermore, SCR evaluations after radiotherapy are a clinical index for comparing treatment planning outcomes [13].

Since secondary cancer development is related to the absorbed dose by the OAR, three-dimensional dose distribution within the irradiated organs can be used to accurately assess SCR incidence. In this regard, the dose-volume histogram (DVH) data is often considered for evaluating the 3D dose distribution inside the intended organs. In modern radiotherapy techniques, the 3-dimensional dose distribution is usually created in a computer-aided treatment planning system (TPS) by employing the patient's computed tomography (CT) data and a specific dose computation algorithm. One of the main concerns relevant to the DVH data is that this clinical parameter structures a non-uniform dose distribution for each intended OAR. On the other hand, a uniform absorbed dose by these OARs is needed for accurate estimation of cancer risk incidence following radiotherapy. In this respect, one can refer to the generalized equivalent uniform dose (gEUD) concept to access such a result. This concept is a dose-volume reduction scheme that shows an equivalent uniform dose relevant to a non-uniform dose distribution inside the considered organ and was proposed by Niemierko [14]. It is worth mentioning that the gEUD formalism was first introduced in addition to the Lyman-Kutcher-Burman (LKB) model of natural tissue complication probability (NTCP) [15–17]. In this regard, the current study aimed to evaluate the SCRs during the 3D-CRT of prostate cancer by calculating the typical absorbed dose in non-target healthy organs and employing the National Council of Radiation Protection and Measurements (NCRP) Report 116 recommendations [18].

MATERIALS AND METHODS

General information and treatment planning

Studied patients: In this study, 39 patients with prostate carcinoma at Firoozgar Hospital were considered from November 2021 to March 2022. The age and weight of the enrolled patients ranged from 52 to 85 years old and 58 to 92 kg, respectively. For all patients, the 3D-CRT technique has been performed by applying the Siemens Primus LINAC with 15 MV nominal energy in photon mode. Additionally, the "Ethics Committee of Aja University of Medical Sciences" gave the current study approval with the registration code IR.AJAUMS.REC.1400.058.

The image data: The obtained data relevant to each patient has been acquired in a supine position by employing a 16-slice CT scanner (Siemens SOMATOM Emotion 16-slice CT scanner). The slice thickness during the scan of the pelvic region was considered to be 3 mm. All patients have received radiotherapy. The demographic information of the studied patients is reported in table 1.

Table 1. Lifetime probabilities of developing fatal secondary malignancies.

Organ	Probability of fatal cancer (% Sv^{-1})
Bladder	0.30
Bone marrow	0.50
Bone surface	0.05
Breast	0.20
Esophagus	0.30
Colon	0.85
Liver	0.15
Lung	0.85
Ovary	0.10
Skin	0.02
Stomach	1.10
Thyroid	0.08
Remainder of body	0.50
Total	5.00

Target volumes delineation: A physicist and an oncologist contoured the external outline for all studied patients in the present study. Using the Eclipse Treatment Scheduling System (Varian Oncology Systems, Palo Alto, CA), an oncologist delineated the prostate, rectum, and bladder in the relevant CT images of each enrolled patient. The specified volumes by the physician were then extended with a margin to generate the planning target volumes (PTV). Except for the posterior part of the prostate (with a 10 mm margin), a 15 mm margin was applied in all directions.

Treatment planning: Following the target and OAR volume delineations, a 3D-CRT technique was considered for all patients to simulate the first stage of treatment (with the prescribed dose of about 70

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Gy). The considered beam arrangement included five separate radiation fields (including anterior-posterior (AP), left anterior oblique (LAO), left posterior oblique (LPO), right anterior oblique (RAO), and right posterior oblique (RPO)). The isocenter was set at the intercept of the central beam axes and located at the PTV center. Beam weights and gantry angles might be changed according to the patient's diameter in the AP and lateral directions. A sample of the implemented beam arrangement for considered treatment plans is shown in figure 1.

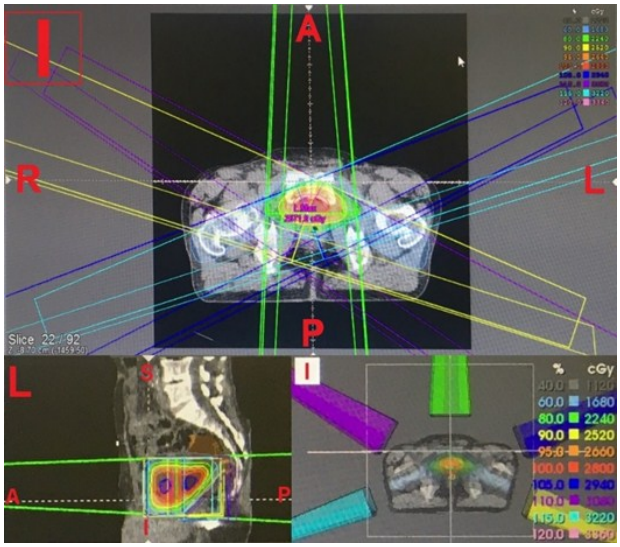

Figure 1. The dose distribution generated by 5 treatment fields (including anterior-posterior, left anterior oblique, left posterior oblique, right anterior oblique, and right posterior oblique) in the 3DCRT of prostate cancer.

The generalized equivalent uniform dose (gEUD) evaluations

The absorbed dose within the contoured organs (bladder and rectum) should be accurately estimated to estimate the risk of developing secondary cancers after prostate cancer radiotherapy. Due to the non-uniform dose distribution inside the OARs during radiotherapy, the gEUD formalism [19] was employed in the current study to estimate the absorbed dose within the contoured out-of-field organs, including the rectum and bladder. The gEUD concept can be quantified through equation 1:

$$gEUD = (\sum_i v_i D_i^a)^{\frac{1}{a}} \quad (1)$$

Here, Di and vi represent the absorbed dose in the ith voxel and the volume fraction of the dose bin relevant to the Di dose, respectively. Equation 1 serves as an example of how to take the volume effects into account [20]. To calculate the gEUD values for the bladder and rectum, the numerical value for the "a" parameter was chosen from the studies conducted by Burman *et al. and Emami et al.* [21,22]. Accordingly, the "a" value was set to 8.3 and 2 for the rectum and bladder, respectively. A fractionated radiotherapy strategy with a 2 Gy dose per fraction was considered for all patients.

Secondary cancer risk estimation

After the gEUD calculation for the bladder and rectum through the corresponding DVH data, the risk of secondary malignancy was estimated using the introduced risk coefficients in the NCRP-116 report [23-29]. By multiplying the recommended coefficients (% per Sv), as listed in table 2, by the received dose to each particular organ, one can calculate the lifetime probabilities of developing fatal secondary malignancies. The introduced risk coefficients in this report are based on the data from Japanese atomic bomb survivors, representing the absolute lifetime risk of developing a fatal secondary cancer weighted over the population of all ages for both sexes [30,31].

Table 2. Calculated gEUD values related to rectum and bladder for 39 patients.

gEUD (Gy)			
Organ	**Minimum**	**Mean**	**Maximum**
Rectum	51.035	60.98±5.6	74.693
Bladder	27.214	53.74±13.2	75.513

Statistical analysis

The current study used Mathematica software version 9.0 to calculate the gEUD values, the standard deviation (SD) around the mean dose value, and secondary malignancies in various studied organs. Since this study aimed only to evaluate the absorbed dose and secondary cancers relevant to prostate cancer radiotherapy, no particular test has been employed for the data analysis.

RESULTS

The generalized equivalent uniform dose (gEUD) evaluations

The obtained DVH data for a selected patient has been shown in figure 2.

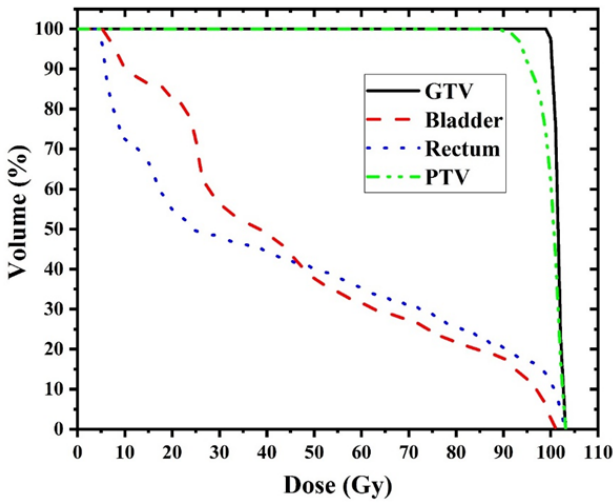

Figure 2. The Dose Volume Histogram (DVH) relate to the treatment plan for prostate cancer.

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With the DVH data for different patients, one can directly calculate the gEUD for the interested organ. The gEUD values corresponding to the bladder and rectum, as a function of "a" parameter, have been shown in figure 3 for some patients considered in this study.

As depicted in figure 3, the gEUD values increase by incrementing the "a" parameter. It should be noted that the gEUD values have been calculated for all studied patients, but due to many results, the obtained gEUD values for the rectum and bladder have been depicted only for three patients.

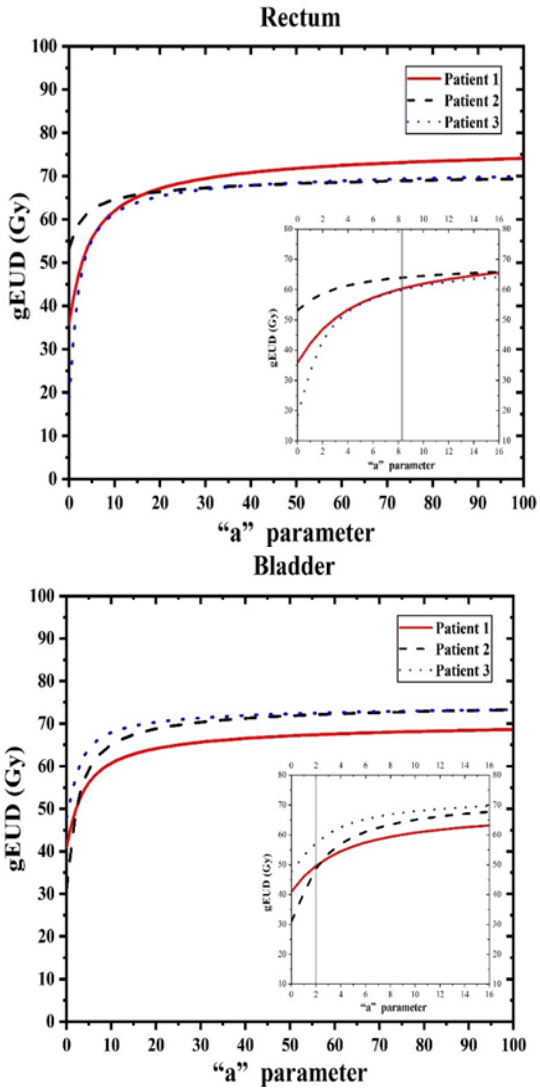

Figure 3. The calculated generalized equivalent uniform dose (gEUD) as the function of parameter "a".

Furthermore, the illustrated results in figure 3 show that the maximum variation range of gEUD values is when the "a" parameter lies within 0–4 and 0–2 for the rectum and bladder, respectively.

The gEUD values related to bladder and rectum for all involved patients (considering "a" parameter as 8.3 and 2 for rectum and bladder, respectively) in the current study (39 ones) have been shown in figure 4.

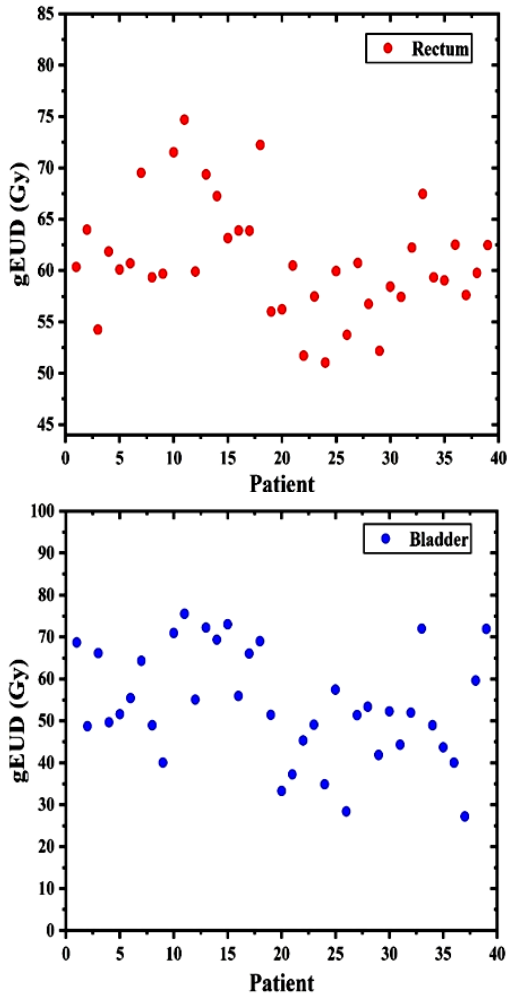

Figure 4. Estimated gEUD values inside the bladder and rectum for all studied patients.

As shown in figure 4, the gEUD values for the rectum range from 50 to 75, while this value varies between 25 and 80 for the bladder. The drawn error bars correspond to one standard deviation around the acquired mean values. The mean gEUD values related to the rectum and bladder have been listed in table 3.

Table 3. Calculated secondary cancer risk in non-target organs associated with the radiotherapy of prostate cancer.

Secondary cancer risk (%)			
Organ	**Minimum**	**Mean**	**Maximum**
Rectum	25.5	30.49±2.8	37.3
Bladder	8.1	16.13±3.9	22.6

According to the reported mean gEUD values in table 3, it can be deduced that the absorbed dose by the rectum is higher than the one for the bladder. This finding is mainly linked to the proximal position of the rectum relative to the prostate compared to the bladder. Consequently, it would be expected that more radiation doses would be delivered to the rectum during prostate cancer radiotherapy.

Secondary cancer risk assessments

As mentioned, the NCRP-recommended cancer

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risk coefficients were employed to estimate the risk of secondary cancer development in the bladder and rectum following prostate cancer radiotherapy. For the equivalent dose calculation, the obtained gEUD values were multiplied by relevant radiation weighting factors (wR) for photons. Since wR for photon radiation is unitary, the equivalent dose will equal the calculated gEUD values in each considered healthy organ (bladder and rectum).

The patient-specific cancer risk values for the rectum and bladder following prostate cancer radiotherapy have been illustrated in figure 5.

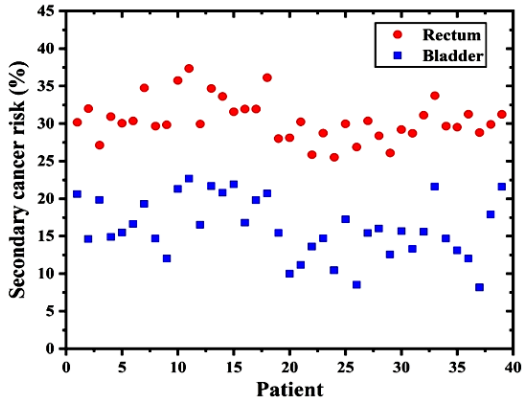

Figure 5. Calculated risk of developing secondary cancer for bladder and rectum after the prostate cancer radiotherapy.

The mean risk of secondary cancer induction in the rectum and bladder was equal to 30.4% and 16.1%, respectively. Such a result clearly shows that the risk of secondary cancer in the rectum is 1.88 orders higher than in the bladder. This fact can be mainly attributed to the higher dose received by the rectum compared to the bladder, which was established during the gEUD calculations in the previous section.

The reported data in table 3 also demonstrates an excellent probability of secondary cancer development in OARs following external radiotherapy for prostate cancer. Therefore, more attention should be paid to reducing the risk of developing secondary cancer in such healthy organs through proper shielding and/or treatment plan optimization.

DISCUSSION

In all radiotherapy modalities, healthy organs are often exposed to radiation. Therefore, developing secondary cancers caused by primary and scattered radiation should be considered a significant side effect of radiotherapy.

A remarkable growth in gEUD values would be observed when the "a" parameter lies within 0–9 and 3–0 for the rectum and bladder (as demonstrated in figure 3). Small "a" values would be relevant to the maximal volume effect, and according to Equation 1, it can be expected that a considerable increment would be seen in the gEUD value. On the other hand, no substantial change would be realized for gEUD when the "a" parameter goes beyond 17 and 4 for the rectum and bladder, respectively. As indicated in figure 3, an almost plateau region would be observed for the gEUD value in this range for both OARs. Large "a" values are equivalent to a minimal volume effect. Accordingly, it can be deduced that no considerable change would be observed in the gEUD value for large "a" values.

Although the exact treatment planning strategy was followed for all enrolled patients in our study during prostate cancer radiotherapy (the Five-Field Technique, as shown in figure 3), different gEUD values resulted for 39 considered prostate patients, as indicated in figure 4. This finding can be due to several factors, including patient size (obesity and thinness), tumor volume, size of organs at risk (full or empty bladder), air cavities in the pelvis, and movement of the genitals [32]. Variations of these physical parameters can change the radiation beam weight and angle of incidence for various patients [33]. Consequently, different dose distribution patterns would be observed for considered OARs, which could finally lead to distinguishing gEUD values for considered patients in the current study.

The results in table 3 demonstrate that the estimated mean gEUD value for the rectum is higher than for the bladder. This finding is mainly because the rectum is more proximal to the prostate than the bladder. Subsequently, it would be expected that more radiation doses would be delivered to the rectum during prostate cancer radiotherapy. Large standard deviations (SD) related to the obtained mean gEUD values are due to different isodose distributions within the rectum and bladder for each studied patient, as discussed previously.

As illustrated in figure 5, the risk of secondary cancer incidence in the rectum is higher than that of the bladder for all studied patients. Two main reasons are considered for this increased secondary cancer risk in the rectum compared with the bladder. The first one is that the received dose inside the rectum during the prostate cancer irradiation is higher than the bladder (as shown in figure 4). The second issue is the higher radiation sensitivity of the rectum in comparison with the bladder, which causes a higher risk coefficient value for this organ (as listed in table 1, the risk coefficient for the rectum and bladder is respectively equal to 0.5 and 0.3% per Sv, as listed by the NCRP-116 report). These two factors finally lead to a higher secondary cancer risk probability for the rectum than the bladder organ.

In addition to the higher SCR probability, it is worth noting that the rectum is a serial organ, while the bladder is considered a serial-parallel organ [34]. Disabling any subunit in serial organs causes the entire organ to fail. In return, organ failure in parallel

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organs may be created when many or all subunits are disabled [35]. This issue is crucial because even if the induced abnormality in the considered OARs (bladder and rectum) following prostate cancer radiotherapy were not cancerous, the severity of the induced abnormality is more evident in the rectum in comparison with the bladder. So, if we seek the risk of non-malignant disorders following prostate cancer radiotherapy, it is also realized that the rectum is more exposed to the abnormality risk.

As demonstrated in figure 5, the cancer risk values for the rectum were higher than those associated with the bladder. On the other hand, if this finding is compared with the obtained DVH data in figure 2, we have encountered a contradiction. In this regard, if we want to talk about the risk of cancer incidence and relevant clinical side effects following the radiotherapy only based on the calculated DVH data for each considered OAR, the bladder is expected to be more exposed to radiation damage and consequent biological side effects. But gEUD-based evaluations and NCRP-116 recommendations give a precisely opposite result.

In Michalis Mazonakis *et al.'s* [36] study, the risk of bladder and secondary rectal cancers after prostate cancer radiotherapy by the VMAT technique has been assessed. In this study, it has been found that in different VMAT techniques, the average organ equivalent dose (OED) of the rectum was 1.2 times higher than that of the bladder. This indicates that the risk of secondary cancer in the rectum is higher than in the bladder.

The risk of SCRs following 3D-CRT, VMAT, and proton therapy has been investigated by Stokkevåg *et al.* [37]. The mean calculated relative risks of VMAT in comparison with IMPT were 1.1 and 1.7 for the bladder, while these values were 0.9 and 1.8 inside the rectum for VMAT and IMPT, respectively. Besides, the obtained results in this study revealed that the risks of radiation-induced bladder and rectal cancers were low in the VMAT technique if exposed at 80 years versus IMPT if exposed at 50 years.

Ted's results on secondary cancers in the present study differ from those calculated in Stokkevåg *et al.* [37]. This discrepancy can be justified because the risk of secondary cancers in the rectum and bladder has been calculated by the NCRP-116 model, which can be employed for all ages, the entire population, and both sexes. In contrast, the calculation of the secondary risk in the Stokkevåg et al. study was based on the biological effects of ionizing radiation (BEIR) VII model, which is the age-specific and site-specification risk model [37]. It is worth noting that there was a limitation associated with the employed risk factors for developing secondary malignancies. The employed coefficients for secondary risk calculation have significant uncertainties concerning the epidemiological data when applied to a particular population [30]. Systematic errors related to the NCRP-116 risk model were unavailable, so these values have not been reported in the present study.

Using the single DVH diagrams for clinical interpretation and estimating the SCR in healthy organs will not be appropriate. Apart from the administered dose, other parameters, including the radiation sensitivity of the intended organ and the uniformity grade of the dose distribution inside the organ, can also contribute to the risk of secondary cancer incidence. The first parameter can be reflected in the reported SCR coefficients in the NCRP-116 report, while the gEUD concept can introduce the second factor. Therefore, considering these two parameters during the SCR estimation following radiotherapy can lead to more promising results.

CONCLUSION

Radiation-induced SCR in the bladder and rectum after radiotherapy for prostate cancer was assessed through the estimation of the gEUD values as well as the NCRP-116 recommendations. The results demonstrated that the risk of secondary cancer induction in the rectum and bladder is remarkable and can reach about 34% and 23%, respectively. Hence, after prostate cancer radiotherapy, the rectum was more vulnerable than the bladder.

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***Author contributions*:**

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