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Technical Note

Estimation of the risk of secondary cancer in rectum and bladder after radiation therapy for prostate cancer using a feasibility dose–volume histogram

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ABSTRACT

We investigated the risk of secondary cancers in rectum and bladder for prostate cancer radiotherapy using a feasibility assessment tool. We calculated the risk of secondary cancer by generating a dose-volume histogram based on an ideal dose falloff function (f-value). This study found a smaller f-value was associated with a lower secondary cancer risk in the rectum but a higher risk in the bladder. The study suggests setting the f-value at 0-0.1 as the optimization goal for the rectum and 0.4 for the bladder is reasonable and feasible for reducing the risk of secondary cancer and other adverse events.

1. Introduction

One of the most important late toxicities caused by prostate cancer radiation therapy is secondary cancer [1–4]. To estimate the risk of secondary cancer, Schneider et al. proposed some models for predicting the risk of secondary cancer from data obtained from patients surviving atomic bombs and patients irradiated for Hodgkin's lymphoma [5–7]. Among these models, the full mechanistic dose–response model, which best considers tissue- and dose-dependent cell biological properties, such as cell destruction and cell regeneration, was used to predict the risk of secondary cancer after EBRT for prostate cancer [8–11]. The full mechanistic dose–response models need not only the prescription dose, number of fractions, parameters of dose–response relationship of secondary cancer induction, and age-modifying factors but also differential dose–volume histograms (DVHs) of each organ. Therefore, since estimating the risk of secondary cancer requires dose calculation using a treatment planning system (TPS), it is not possible to predict the occurrence of secondary cancers before dose calculation. If treatment planners can recognize the risk of secondary cancer occurrence in advance, similar to dose constraints for genitourinary (GU) and gastrointestinal (GI) toxicity, it can lead to efficient treatment planning. However, to the best of our knowledge, no such study exists.

PlanIQ (Sun Nuclear Corp., Melbourne, FL, USA) is software designed to provide patient-specific estimates of the feasibility of reducing dose in radiotherapy dose-volume histograms [12–18]. The PlanIQ software takes into account anatomical geometries and beam energy to determine the feasibility of reducing the dose to organs-at-risk (OARs). The feasibility DVH (FDVH) tool of PlanIQ provides four DVH regions for an OAR based on the ideal target-dose conformity and dose falloff around the target (Fig. 1 (a)). These regions include *impossible* ($f < 0$), *difficult* ($f = 0$–0.1), *challenging* ($f = 0.1$–0.5), and *probable* ($f = 0.5$–0.9), and are compartmentalized by a parameter known as the feasibility value (f-value). The f-values for each OAR are defined as values converted based on the distance between the FDVH ($f = 0$) and a coordinate, which is derived from a specific dose and the cumulative percent volume. Thus, by using FDVH, it is possible to obtain the differential DVH of each organ before dose calculation, and the risk of secondary cancer occurrence can be verified in advance.

In this study, the risk of secondary cancer and the achievement rates of dose constraints in the rectum and bladder of patients undergoing radiation therapy for prostate cancer were calculated using f-value of FDVH. The aim of this study was to investigate the optimal f-value for reducing the incidence of secondary cancer while meeting dose constraints.

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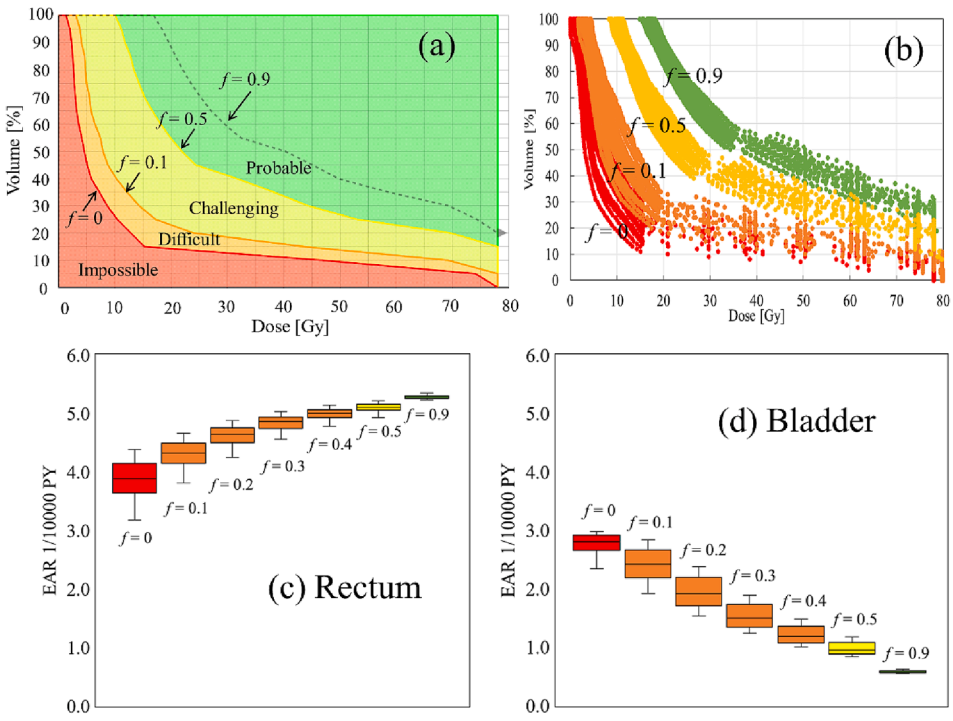

Fig. 1. (a) An example of feasibility dose–volume histograms (FDVH) for the normal rectum in a patient. The four DVH regions, namely impossible (red), difficult (orange), challenging (yellow), and probable (green), are compartmented by the *f*-value. (b) FDVH of the bladder in 20 patients. Excess absolute risk (EAR) in each *f*-value of radiation-induced secondary cancer based on the full mathematical model in 20 patients with (c) rectum and (d) bladder cancers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

2.1. Patients

Twenty patients who underwent radiation therapy for prostate cancer at our hospital between 2008 and 2017 were randomly selected. The clinical target volume (CTV) was defined as the entire prostate and proximal seminal vesicle. The CTV with a 3–6-mm margin was defined as planning target volume 1 (PTV1). Outside PTV1, the distal seminal vesicle with a 5-mm margin was defined as PTV2. The patients were instructed to maintain a full bladder and empty rectum before simulation and each treatment. The median volume and range were 18.5 mL (range, 12.8–50.7 mL) in the prostate, 42.0 mL (range, 30.6–106.8 mL) in the rectum, and 176.4 mL (range, 79–351.8 mL) in the bladder. The prescribed dose was 78 Gy/39 fractions for PTV1 and 64 Gy/39 fractions for PTV2, and 95% of the PTV were administered the prescribed dose. The intensity-modulated radiation therapy plans were created using one or two coplanar arcs with a photon energy beam of 6 MV by RayStation version 10.0 (RaySearch Laboratories AB, Stockholm, Sweden). The dose constraints for the rectum and bladder, which were based on a previous trial [19], were as follows: (1) rectum: the percentage of the rectum covered by at least 70 Gy (V_{70Gy}): <15%, $V_{60Gy} < 50\%$, $V_{50Gy} < 50\%$, and $V_{40Gy} < 70\%$; (2) bladder: $V_{60Gy} < 25\%$, and $V_{50Gy} < 50\%$. This study was approved by the local ethics committee (no. 2020-1-556).

2.2. Secondary cancer risk

Four dose–response models have been reported to determine the relationship between the dose and the risk of radiation-induced secondary cancer: linear, bell-shaped, plateau, and full mathematical models [8]. For the most accurate estimation of the risk of secondary cancer, a full mathematical model was used as follows:

$$RED(D) = \frac{e^{\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R}D}\right) \quad (1)$$

where risk equivalent dose (RED) is the dose–response relationship for radiation-induced cancer in units of dose. It is assumed that the tissue is irradiated with a fractionated treatment schedule of equal dose fractions d up to a dose D. R is a repopulation parameter ranging between 0 and 1 ($R = 0$: no repopulation; $R = 1$: full repair of repopulation).

$$\alpha' = \alpha + \beta \frac{D}{D_T} d_T \quad (2)$$

The number of cells is reduced by cell killing, which is proportional to α', and is defined using the linear quadratic model, assuming $\alpha/\beta = 3$ Gy for all tissues. D_T is the prescribed dose, and d_T is the fraction dose. The excess absolute risk (EAR) can be calculated using the organ equivalent dose (OED) based on data on DVHs and RED, as follows:

$$OED = \frac{1}{V_T}\sum_i V(D_i) RED(D_i) \quad (3)$$

where V_T is the total organ volume and $V(D_i)$ is the i-th dose volume of the OAR that is irradiated to dose D_i. EAR described the absolute difference in cancer rates between persons exposed to dose d and those unexposed to a dose beyond the natural dose exposure per 10,000 person-years per Gy. EAR was calculated as follows:

$$EAR(D, agex, agea) = OED \times \beta_{EAR} \times e^{\left(\gamma_e (agex-30) + \gamma_a \ln\left(\frac{agea}{70}\right)\right)} \quad (4)$$

where β_{EAR} is the slope of the dose–response curve at low doses, x is the age at exposure, and a is the attained age. γ_e and γ_a, which are derived by Preston *et al.* [20], are the age-modifying parameters. To remove the EAR variability related to the varying age of irradiated patients, the EAR was calculated for all patients assuming that it was for patients irradiated at the age of 60 years and reached an age of 80 years. These parameters were based on the previously published cancer risk data from A-bomb survivors [21,22] and patients receiving radiation therapy for Hodgkin's lymphoma [6,23,24].

2.3. Feasibility DVH

To predict the FDVH from patient computed tomography images and structures, PlanIQ was used. Based on an ideal dose falloff from the

Table 1
Number of patients (n = 20) who achieved the dose constraints and achievement rates of rectum and bladder dose constraints at $f = 0$, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.9.

Organ at risk	Variation acceptable	$f = 0$	$f = 0.1$	$f = 0.2$	$f = 0.3$	$f = 0.4$	$f = 0.5$	$f = 0.9$
Rectum	$V_{70Gy} < 15\%$	19	18	16	10	4	1	0
	$V_{60Gy} < 50\%$	20	20	20	20	20	20	20
	$V_{50Gy} < 50\%$	20	20	20	20	20	20	20
	$V_{40Gy} < 70\%$	20	20	20	20	20	20	20
	Achievement rates [%]	99 (79/80)	98 (78/80)	95 (76/80)	88 (70/80)	80 (64/80)	76 (61/80)	75 (60/80)
Bladder	$V_{60Gy} < 25\%$	20	20	20	20	18	7	0
	$V_{50Gy} < 50\%$	20	20	20	20	20	20	20
	Achievement rates [%]	100 (40/40)	100 (40/40)	100 (40/40)	100 (40/40)	95 (38/40)	67 (27/40)	50 (20/40)

f: feasibility value.

prescription dose at the target boundary (i.e., benchmark dose distribution), the software provided four DVH areas of 20 patients for each structure according to the *f*-value (e.g. bladder, Fig. 1(b)). In other words, the *f*-value ranges between 0 and 0.9, and smaller values indicate greater difficulty in achieving the goal. In 20 patients, the EARs of the rectum and bladder were calculated using the following *f*-values ($f = 0$, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.9, respectively). Similarly, the relationship between the *f*-value and the achievement rates of dose constraints was evaluated.

3. Results

Fig. 1(c) and (d) shows the relationship between the *f*-values and the EAR for the rectum and bladder. The median EAR for the *f*-values 0, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.9 was 3.9 (range, 3.2–4.4), 4.3 (3.8–4.7), 4.6 (4.2–4.9), 4.9 (4.6–5.0), 5.0 (4.8–5.1), 5.1 (4.9–5.2), and 5.3 (5.2–5.3), respectively, in the rectum and 2.8 (2.3–3.0), 2.4 (1.9–2.8), 1.9 (1.5–2.4), 1.5 (1.2–1.9), 1.2 (1.0–1.5), 1.0 (0.8–1.2), and 0.6 (0.5–0.6), respectively, in the bladder. The rectum had a smaller EAR as the *f*-values decreased. In contrast, in the bladder, the smaller the *f*-value, the larger the EAR.

Table 1 shows the relationship between the *f*-value and the achievement rate of dose constraints. For both the rectum and bladder, the achievement rate of the dose constraint was higher for smaller *f*-values. Specifically, the achievement rate exceeded 95% for the rectum with *f*-values ranging from 0 to 0.2 and for the bladder from 0 to 0.4. This means that in some cases, DVHs with an *f*-value of 0.3 or higher for the rectum and an *f*-value of 0.5 or higher for the bladder will not be able to achieve some of the dose constraints.

4. Discussion

Using the FDVH, the risk of secondary rectal and bladder cancers in patients who underwent radiation therapy for prostate cancer was estimated before dose calculation using a TPS. GI and GU adverse events related to prostate cancer radiation therapy, other than secondary cancer, are known. Rectal bleeding is correlated with the volume irradiated (60–70 Gy); thus, reducing areas exposed to high radiation doses is important [25]. Because the achievement rate of rectal dose constraints increases as the *f*-value decreases (Table 1), developing a treatment plan with low *f*-value as much as possible is necessary. In addition, because the risk of secondary rectal cancer is higher at high doses than at low doses [8], the EAR decreased by decreasing the *f*-value. Studies have proposed using the *f*-value of 0.1 as the first choice for prostate radiation therapy planning [16,17]. Therefore, creating a treatment plan using *f*-values of 0–0.1 (i.e., difficult area) is necessary to reduce the risk of secondary cancer and GI adverse events.

GU adverse events are correlated with high radiation doses [26]. Therefore, a smaller *f*-value is also effective in reducing GU adverse events. In contrast, regarding the bladder, the smaller the *f*-value, the higher the EAR. This is because the radiation dose related to the highest risk of secondary bladder cancer is approximately 4 Gy [8]. This result is described by the cell killing hypothesis and agrees with the risk of secondary thyroid and kidney cancers [27]. Therefore, as the *f*-value decreases, the risk of secondary cancer increases. Thus, creating a plan using acceptably high *f*-values while achieving dose constraints is necessary. In the bladder, the maximum *f*-value for which the achievement rate exceeded 95% was 0.4. In the clinical plan for the 20 patients examined in this study, the dose constraints were achieved in all patients, and the median EAR and *f*-value in the bladder were 1.31 and 0.37, respectively. As shown above, setting the *f*-value at 0.4 (i.e., challenging area) as the goal for the optimization parameters in the bladder is reasonable and feasible to reduce the risk of secondary cancer and other adverse events.

The incidence rates of secondary rectal and bladder cancers in patients who had undergone radiation therapy more than 5 years ago were significantly higher, 1.9 and 1.5 times, respectively, than in the surgical group [3]. Especially, the incidence of secondary cancer in the postoperative irradiation group was even more pronounced because the OAR volume contained in the irradiation field was large [1,28]. Therefore, for patients expected to have long-term survival, creating a treatment plan that reduces the occurrence of secondary cancer and GI and GU events is necessary.

A limitation of this study is the absence of clinical data on the incidence of secondary cancers and adverse events when treatment is planned with *f*-values added to the dose constraints. In addition, sample size of 20 is small, limiting statistical power. Moreover, the study was conducted at a single institution, which may limit the generalizability of our results beyond the population studied. Therefore, to ensure the robustness of our results, larger multicenter studies with a sufficient sample size are required. Such studies can help to better understand the risks of secondary cancer after radiotherapy and improve the quality of treatment planning and management of patients.

In conclusion, the *f*-value could estimate the incidence of secondary rectal and bladder cancers after radiation therapy for prostate cancer. The EAR calculated using the full mathematical model decreased as the *f*-value decreased in the rectum. Conversely, in the bladder, the smaller the *f*-value, the larger the EAR. Based on the results of this study, it seems reasonable and realistic to set $f = 0$–0.1 as the optimization goal for the rectum, and $f = 0.4$ for the bladder, in order to reduce the risk of secondary cancer and other adverse events.

5. Ethics approval and informed consent

This study was approved by the local ethics committee (no. 2020-1-556).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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