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Study on the physical factors related to the exposure dose to organs at risk from radiotherapy for cervical cancer patients

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► ***Original article***

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ABSTRACT

***Background*:** This research was performed to analyze the relationship among the physical factors of cervical cancer patients and the $V_{40\text{-}x}$ (volume of the *x* receiving 40 Gy, *x* is replaced by bladder or rectum below). In addition, the methods to control the factors affecting these related physical parameters are comprehensively discussed so that the side effects of radiotherapy can be reduced. ***Materials and Methods*:** Sixty cervical cancer patients treated with volume-modulated-arc therapy (VMAT) were selected. Related physical parameters of the planning target volume (PTV), rectum, and bladder were collected. The Spearman analysis method was used to discuss the relationship between the physical parameters and $V_{40\text{-}x}$. ***Results*:** The parameter of $D_{max\text{-}rectum}$ (max dose of rectum) and $V_{bladder}$ (volume of the bladder) were significantly negatively correlated with $V_{40\text{-}rectum}$ and $V_{40\text{-}bladder}$, respectively. In addition, we found three dosimetric parameters and four parameters were significantly positively correlated with $V_{40\text{-}rectum}$ and $V_{40\text{-}bladder}$. A reduction in $V_{40\text{-}x}$ of the organs at risk (OARs) was also displayed in the redesigned planning dose images and the dose-volume histograms (DVH). ***Conclusions*:** It is recommended that patients maintain a filled bladder during localization and radiotherapy. It is also recommended that patients maintain an empty rectum during localization and radiotherapy to ensure the stability of the target. According to the correlation of the physical parameters obtained from the results, medical physics can reduce the $V_{40\text{-}x}$ more easily during planning design by specifically controlling some physical parameters, and this can reduce radiation toxicity more effectively.

INTRODUCTION

Cervical cancer is the fourth main cause of cancer mortality in women in the world [1, 2]. The five-year survival rate of cervical cancer is 66.1% [3]. Studies have shown that radical radiotherapy for patients with early cervical cancer (stage I to IIa) has the same curative effect as radical surgery, and patients with high-risk factors after surgery require adjuvant radiotherapy [4]. For locally advanced cervical cancer (stage IIb to IVa), radiotherapy and chemotherapy should be used as standard treatments for locally advanced cervical cancer [1, 5]; therefore, radiotherapy played an important position in the treatment of cervical cancer [1, 6].

Although radiotherapy is effective in controlling tumors, it does have certain side effects. Acute enteritis occurred for most patients with cervical cancer when they were treated using vitro radiotherapy combined with intracavitary radiotherapy [7]. In addition, the incidence of moderate-to-severe radiation proctitis ranged from 5.3% to 15.6%, and the incidence of moderate-to-severe radiation cystitis ranged from 2.48% to 5.6% [8]. These side effects were the primary reasons for the delay, interruption, and poor quality of life of patients who have cervical cancer undergoing radiotherapy [9]. Previous studies have evaluated the correlation between the dose and the radiation toxicity, and the results showed that the exposure dose to organs at risk (OARs) was significantly related to the risk of side effects from radiotherapy [10]. Among them, $V_{40\text{-}rectum}$ (volume of the rectum receiving 40 Gy or more) was the primary influencing factor for acute radiation proctitis. $V_{40\text{-}bladder}$ and $V_{50\text{-}bladder}$ (volume of the bladder receiving 40 Gy and 50 Gy or more, respectively) were the primary factors for the occurrence of radiation cystitis [11]. Therefore, the reduction of $V_{40\text{-}x}$ (volume of the x receiving 40 Gy, x is replaced by bladder or rectum below) play an important part in reducing radiotherapy toxicity and improving the treatment effect. However, according to daily work experience, it is sometimes not easy for medical physics to reduce $V_{40\text{-}x}$ in designing radiotherapy plans. It may take a lot of planning design time, and sometimes it may be necessary to sacrifice other dose constraints during planning design. So, it is necessary to find more methods to

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reduce $V_{40\text{-}x}$ effectively.

Currently, there have been only a few studies that have reported on methods to reduce $V_{40\text{-}x}$ from the perspective of clinical and physical factors. In this study, we select some clinical and physical parameters of 60 patients undergoing radiotherapy for cervical cancer that may influence the $V_{40\text{-}x}$ according to our experience and the results of several studies. We then analyze the relationship between these related factors and the $V_{40\text{-}x}$. The purpose of this study was to find methods to comprehensively control the factors that affect these related physical parameters and to provide some clinically feasible methods for reducing $V_{40\text{-}x}$ more effectively so that the side effects can be reduced, and the treatment effect can be improved.

MATERIALS AND METHODS

Patients' selection

Between December 2020 and December 2021, 60 patients with cervical cancer who were treated with radiotherapy were enrolled in this retrospective study. The prerequisites for enrolling patients are described as follows: ① no computed tomography (CT) scan contraindications; ② no serious diseases (except for cervical cancer); and ③ patients had a Karnofsky performance status score (KPS) of greater than 70. Due to the higher prescribed doses for lymph nodes and the greater impact on the OARs, this study did not consider the patients with gross tumor volumes of the cervical lymph nodes (GTV_{nd}). This study was approved by the medical ethics committee of Longyan First Affiliated Hospital of Fujian Medical University (registration number: Ethical review of scientific research number 73, registration date: December 18, 2020) and was based on the Helsinki Declaration. Informed consent was obtained from all of the subjects prior to the study. The patient characteristics are shown in table 1.

Table 1. Patient characteristics.

Number of patients	60
Age	mean age±standard deviation: 48.3±14.7 yr; range, 29–81 yr
Tumor site	Cervix
Gender	Female
Weight	Median (Range): 53 (46–63)
FIGO stage	IB2: 03; II A: 14; II B: 16; III A: 18; III B: 07; IV A: 02

Patient simulation and contouring

All of the patients were scanned in a dorsal decubitus, with both hands placed on the forehead, and a body positioning bag (R7414-25NL, Klarity, China) were selected to fix the position. The CT simulator (Discovery CT 750 HD, GE, USA) performed a plain scan when the patient was breathing calmly. The scanning range was based on the specific conditions of the patient, with a range of at least 2 cm from the lower edge of the twelfth thoracic vertebra to the lower edge of the femoral lesser trochanter, which is equivalent to 2 cm below the ischial tuberosity. The thickness of the scanning slice was 2.5 mm. All of the scanned images were sent to the treatment planning system (TPS) (Monaco 5.1, Elekta, Sweden) for radiotherapy planning.

All of the structures, including the gross tumor volume (GTV), the OARs, and the clinical tumor volume (CTV), were delineated by experienced oncologists referring to the International Commission for Radiation Units and Measurements (ICRU) No. 89 [1, 12]. The region of CTV contained the paravaginal tissues and proximal vagina [13]. The planning target volume (PTV) was produced by enlarging an isotropic margin of 8 mm to the CTV [13].

Treatment planning and techniques

All of the plans were created with dual-arcs for 6-MV photons using the Elekta TPS. The prescription was set to 28 fractions of 1.8 Gy, 1 time/day, 5 days/week, divided into 28 times, totaling 50.4 Gy. The specific dose requirements are shown in table 2.

In addition, the plans were administered using a LINAC accelerator (Synergy, Elekta, Sweden). Volume -modulated-arc therapy (VMAT) for cervical cancer was performed 1/day, 5/week, with a total treatment time of approximately 5.6 weeks.

Table 2. Dose restrictions for the target and the OARs.

Target or OARs	Dose restrictions
PTV	$V_{100\%PD} \geq 95\%$, $V_{110\%PD} < 5\%$
Rectum	$V_{46} \leq 50\%$
Bladder	$V_{46} \leq 50\%$
Small intestine	$V_{30} \leq 40\%$
Femoral head	$V_{45} \leq 5\%$

PD (prescribed dose); V100%PD (the PTV volume receiving 100% of the PD); V110%PD (the PTV volume receiving 110% of the PD); and Vn (the volume receiving n Gy or more) (12).

Data processing

For the PTV, the evaluation parameters included $D_{max\text{-}PTV}$, $D_{mean\text{-}PTV}$ (maximum and mean dose of PTV, respectively), V_{PTV} (volume of the bladder), and $V_{53\text{-}PTV}$ (volume of the PTV receiving 53 Gy or more). For normal tissues x, the analysis included $V_{40\text{-}x}$, $V_{46\text{-}x}$ (volume of the x receiving 46 Gy), V_x (volume of x), $D_{max\text{-}x}$ and $D_{mean\text{-}x}$ (maximum and mean dose of x, respectively), $V_{PTV\cap x}$ (the volume of x at the intersection of the target), $V_{PTV\cap x}/V_x$ (the ratio of the intersection volume of x and PTV to x volume), $D_{mean\text{-}PTV\cap x}$ (mean dose of the intersection of PTV and x), and $L_{PTV\sim x}$ (distance between the center of x and the center of PTV).

Statistical analysis

The statistical analysis was performed using SPSS 16.0 (IBM, America). Statistical parameters of the PTV, bladder, and rectum are shown in table 3. All of

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the data are expressed as mean±standard deviation. The Spearman correlation method was used to analyze the correlation between $V_{40\text{-}x}$ and the other parameters, and it was considered statistically significant when the value of *P* was less than 0.05

Table 3. Statistical values of the PTV, bladder, and rectum.

Structure	Parameter	Value	Structure	Parameter	Value
Bladder	$V_{40\text{-bladder}}$	54.05±10.05%	Rectum	$V_{40\text{-rectum}}$	57.90±7.74 %
	$V_{46\text{-bladder}}$	40.97±10.32%		$V_{46\text{-rectum}}$	44.42±6.57 %
	$V_{bladder}$	247.06±179.73 cm^3		V_{rectum}	59.99±36.78 cm^3
	$D_{max\text{-bladder}}$	53.90±0.58 Gy		$D_{max\text{-rectum}}$	53.31±0.60 Gy
	$D_{mean\text{-bladder}}$	39.28±2.46 Gy		$D_{mean\text{-rectum}}$	40.16±1.45 Gy
	$V_{PTV\cap bladder}$	54.94±25.73 cm^3		$V_{PTV\cap rectum}$	20.83±12.18 cm^3
	$V_{PTV\cap bladder}/V_{bladder}$	0.27±0.11		$V_{PTV\cap rectum}/V_{rectum}$	0.36±0.07
	$D_{mean\text{-}PTV\cap bladder}$	51.23±0.18 Gy		$D_{mean\text{-}PTV\cap rectum}$	50.29±0.24 Gy
	$L_{PTV\sim bladder}$	5.19±1.42 cm		$L_{PTV\sim rectum}$	7.15±0.86 cm
PTV	V_{PTV}	862.80±100.61 cm^3	PTV	$D_{max\text{-PTV}}$	55.47±0.52 Gy
	$V_{53\text{-PTV}}$	9.41±4.54%		$D_{mean\text{-PTV}}$	51.68±0.20 Gy

RESULTS

Analysis results of the related factors of the $V_{40\text{-bladder}}$

As shown in table 4, the parameters of $V_{46\text{-bladder}}$, $D_{mean\text{-bladder}}$, $D_{mean\text{-}PTV\cap bladder}$, and $V_{PTV\cap bladder}/V_{bladder}$ were significantly positively correlated with $V_{40\text{-bladder}}$. $V_{bladder}$ was significantly negatively correlated with $V_{40\text{-bladder}}$, and there was no significant relation for other physical parameters with $V_{40\text{-bladder}}$

Table 4. Relative factors of the V40-bladder and V40-rectum.

Object of Spearman correlation analysis	Physical parameters	*r*	*P* value
$V_{40\text{-bladder}}$	$V_{46\text{-bladder}}$	0.857	0.001
	$D_{mean\text{-bladder}}$	0.919	0
	$D_{mean\text{-}PTV\cap bladder}$	0.775	0
	$V_{PTV\cap bladder}/V_{bladder}$	0.744	0.001
	$V_{bladder}$	-0.432	0.017
$V_{40\text{-rectum}}$	$V_{46\text{-rectum}}$	0.932	0
	$D_{mean\text{-rectum}}$	0.878	0
	$D_{mean\text{-}PTV\cap rectum}$	0.924	0.001
	$D_{max\text{-PTV}}$	-0.420	0.021

Analysis results of the related factors of $V_{40\text{-rectum}}$

As shown in table 4, the parameters of $V_{46\text{-rectum}}$, $D_{mean\text{-rectum}}$, and $D_{mean\text{-}PTV\cap rectum}$ had significant positive correlations with $V_{40\text{-rectum}}$. The parameter of $D_{max\text{-PTV}}$ had a significant negative correlation with $V_{40\text{-rectum}}$, and the other physical parameters had no significant correlation with $V_{40\text{-rectum}}$.

Based on the above analysis, we redesigned radiotherapy plan B by focusing on controlling $V_{46\text{-bladder}}$, $D_{mean\text{-bladder}}$, $D_{mean\text{-}PTV\cap bladder}$, $V_{46\text{-rectum}}$, $D_{mean\text{-rectum}}$, and $D_{mean\text{-}PTV\cap rectum}$. A comparison of the dose distribution of the OARs and $V_{40\text{-}x}$ between plans B with the patient's original radiotherapy plan A is shown in figure 1, respectively. The dose-volume histograms (DVH) of bladder, rectum and PTV are shown in figure 2.

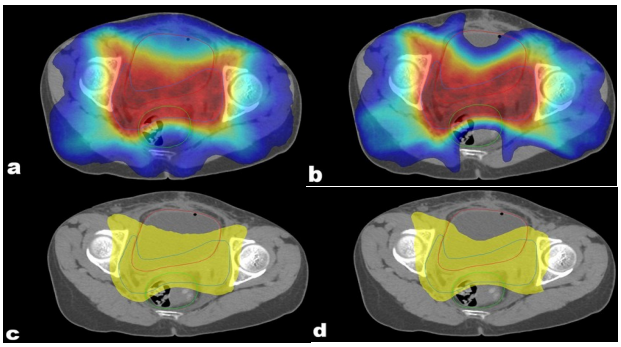

Figure 1. Dose distributions of **(a)** plan A and **(b)** plan B. Different color regions in the plans demonstrate the exposed radiation doses. The yellow color represents the range of V40 in **(c)** plan A and **(d)** plan B.

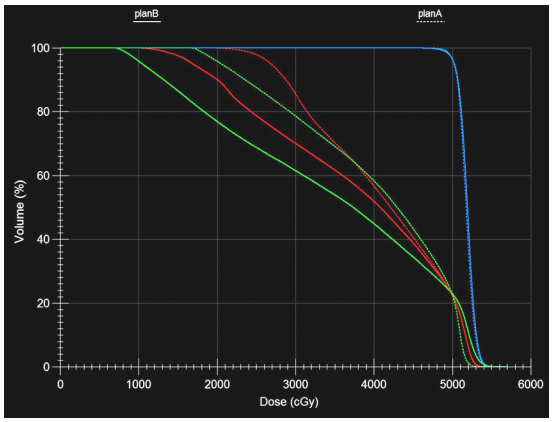

Figure 2. Comparison of dose-volume histograms between plan A and plan B. The red line, the green line, and the blue line represent the dose-volume relationship for the bladder, the rectum, and the PTV, respectively. The solid line and the dotted line show the dates of plan A and plan B.

As can be intuitively seen from the planning images and dose-volume histograms (DVH), the dose control of the OARs in plan B was more effective than that of plan A, especially for the reduction of $V_{40\text{-}x}$.

DISCUSSION

In recent years, there are an increasing number of young patients with cervical cancer, and some of them have to delay or interrupt radiotherapy due to the side effects of the treatment [14]. Many studies have attempted to control the exposure dose of the OARs from all aspects so as to reduce the side effects of radiotherapy.

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Chen *et al.* [15] studied the impact of changes in the volume and spatial position of the CTV and the OARs on the dose distribution of the OARs. They proposed that adaptive radiotherapy (ART) should be used to reduce the exposure dose of the OARs. After an on-line modification of the plan, the dose of each OAR was reduced to varying degrees. However, for busy radiotherapy centers, this is a time-consuming method for medical staff and it is certain to produce difficulties in actual clinical practice.

In a study recently completed by Naik *et al.*, [16, 17] they compared the effects of different radiotherapy methods, such as three dimensional conformal radiation therapy (3D-CRT), dynamic intensity-modulated radiotherapy (Dmlc-IMRT), static intensity-modulated radiotherapy (Step & shoot-IMRT), and VMAT on the dose distribution of the OARs in cervical cancer [1]. The doses of 33% and 48% of the volume for the rectum and the bladder was all reduced in IMRT compared to 3D-CRT [16]. Among the three IMRT technologies, VMAT has the shortest treatment time; VAMT radiotherapy was also used in this study.

Li *et al.* [18] found that bladder filling significantly reduced the average bladder dose, resulting in an average reduction of V_{40} by 38%, and V_{45} (volume receiving 45 Gy) by 31%. Wang *et al.* [19, 12] believed that there was no significant difference in the radiation dose of the rectum and small intestine in different body positions. The exposure dose to the bladder in the prone position was slightly lower than that in the supine position. It is important for patients with cervical cancer to keep the bladder filling, and this can significantly reduce the dose to the small intestine and the bladder. Similarly, the same conclusion for the bladder was found by Buchali *et al.* [20]. They also noted that the filling degree of the rectum had no significant effect on its irradiation dose. These findings were consistent with the results of the correlation analysis results between $V_{40\text{-}x}$ and V_x in our study. Hence, we recommend that patients keep the rectum empty during positioning and radiotherapy to ensure the stability of the target area. In addition, it is recommended that a patient with cervical cancer drink 600 ml water about 30 minutes prior to CT positioning and radiotherapy in order to ensure the filling degree of the bladder. Also, the filling degree should be the same as much as possible, but this is not easy. Recent studies [21, 22] have mentioned a variety of methods to strictly control the filling degree of the bladder, such as injecting the same amount of liquid every time through the indwelling catheter, emptying the bladder, and verifying the bladder volume every time using cone-beam computed tomography (CBCT). Each method has its disadvantages, such as the long-term indwelling of the urinary catheter that increases the risk of cystitis and emptying the bladder increases the exposure dose of the bladder wall. In our study, for patients whose urinary system was damaged and unable to hold urine due to partial surgery, it is recommended to empty the bladder to ensure the stability of the target area, and this may cause a higher $V_{40\text{-bladder}}$ due to a lower $V_{PTV\cap bladder}/V_{bladder}$. Hence, our study suggested that the medical physics should focus on controlling the parameters of $V_{46\text{-bladder}}$, $D_{mean\text{-}bladder}$, and $D_{mean\text{-}PTV\cap bladder}$ during the process of planning designation. It is recommended that the $V_{40\text{-bladder}}$ should be controlled below 54.05% (the average value obtained in our study).

Mo *et al.* [23] confirmed that the severity of acute radiation rectal reaction can be reduced by reducing the average rectal irradiation dose and V_{40} and V_{50} during external radiation. Our study recommended that medical physics should focus on reducing the parameters of $V_{46\text{-rectum}}$, $D_{mean\text{-}rectum}$, and $D_{mean\text{-}PTV\cap rectum}$ during the optimization of treatment planning so as to reduce the $V_{40\text{-rectum}}$ more simply. It is recommended that the $V_{40\text{-rectum}}$ should be controlled below 57.90% (the average value obtained in our study). We also found a significant negative correlation between $D_{max\text{-}PTV}$ and $V_{40\text{-rectum}}$, suggesting that the rectum near the PTV will have a greater dose drop due to the higher $D_{max\text{-}PTV}$. Hence, when the $D_{max\text{-}PTV}$ is much lower than 110% of the prescribed dose, the restrictions for the maximum dose of the PTV can be appropriately relaxed. Then the $V_{40\text{-rectum}}$ can be reduced more easily during planning optimization for medical physics.

One of the limitations of our study was the relatively small sample size. In our future work, we will increase the sample size, increase the physical parameter studies, and track the side effects of radiotherapy.

CONCLUSIONS

During clinical cervical cancer CT positioning and radiotherapy, we recommend that patients maintain the bladder filling and keep the rectum empty. According to our analysis of correlation among various physical parameters and a comparison of plan A and redesigned plan B, it was easier to reduce the $V_{40\text{-}x}$ during planning design by specifically controlling some physical factors. This will reduce the toxicity and side effects on the rectum and bladder more effectively during radiotherapy.

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